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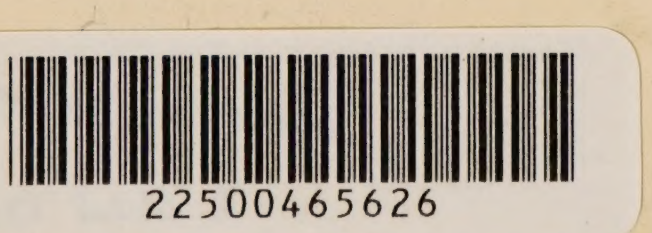

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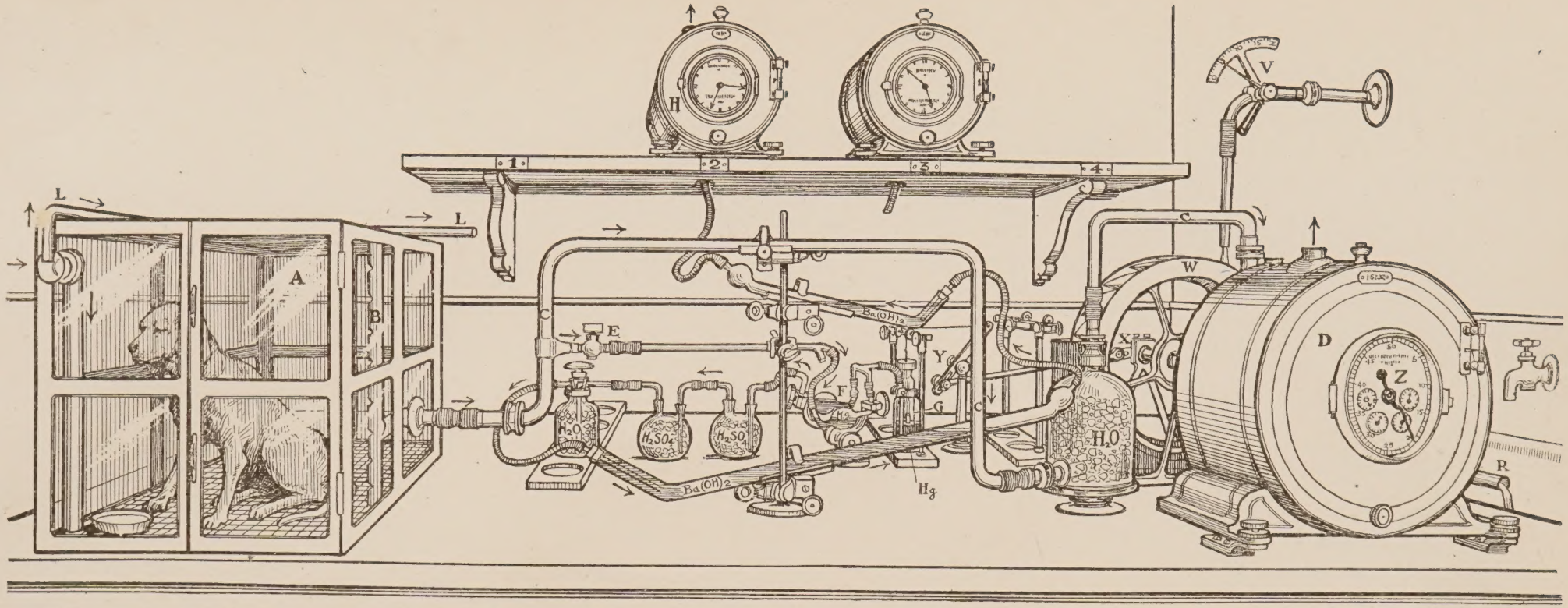

The smaller respiration apparatus of Pettenkoffer and Voit. Air enters the cage, A, at the upper left-hand corner. It is drawn out through openings in the tube B (so spaced as to insure thorough diffusion) through the tube, C, and the large H_2O flask, where it is saturated with moisture, to the gas meter, D, where it is measured. The meter is driven by a water wheel, W, rotated at a uniform rate of speed by a constant head of water pressure, V. At E a side tube leads off from C conveying a sample of cage air for analysis. This air is drawn through a mercury valve, F, by means of the mercury pump, G. The latter is operated by the mechanism, X, Y, connected with the water wheel. From the valve F, this air passes through two H_2SO_4 flasks and is then saturated with moisture so as to prevent loss of water from the $Ba(OH)_2$ tubes. Of course, the air, as it leaves the $Ba(OH)_2$ tubes, is saturated with moisture, and is measured by the small gas meter, H, just as in the case of the large meter, while in this saturated condition. A duplicate sample is led off at the same time through another branch of the tube, E, and through another system of vessels to the gas meter at 3. Through the branches of the tube, L, duplicate samples of the air which enters the cage are drawn in the same manner to similar valves, and then through similar vessels and tubes to meters placed at 1 and 4. (Tigerstedt's "Human Physiology".)

THE

ELEMENTS OF THE SCIENCE

OF

NUTRITION

BY

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To the Memory of

CARL VON VOIT

Master and Friend

From whom the Author received the Inspiration

of his Life's Work

this Volume is dedicated.

"The greatest joy of those who are steeped in work and who have succeeded in finding new truths and in understanding the relations of things to each other, lies in work itself."

Carl von Voit.

PREFACE TO THE SECOND EDITION.

This, the second edition differs chiefly from its predecessor in containing facts which have been brought to light during the past three years.

The aim of the book is to review the scientific substratum upon which rests the knowledge of nutrition both in health and in disease. Throughout, no statement has been made without endeavoring to give the proof that it is true.

The widespread interest in the subject of nutrition at the present time leads the author to hope that this book may prove of value to the student of dietetics and to the clinical physician.

Laboratory methods to explain the inner processes in disease have been applied to hospital patients for twenty years or more in Germany, but in the United States little has been done in this regard. If such investigations are in any way promoted by their discussion here, this writing will not have been in vain.

On a previous occasion the author collected the more important information concerning the life history of the mineral constituents of the body for the American Text Book of Physiology, and the subject has been allotted but little space in this volume.

The author would apologize to all whose claims of priority of discovery have not been duly recognized.

He wishes to express his great obligation to a former pupil, Dr. Margaret B. Wilson, who has painstakingly corrected the manuscript and proof. He gratefully acknowledges the kind encouragement of his former colleagues at the University and Bellevue Hospital Medical College and the helpful criticism of many friends.

GRAHAM LUSK.

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UNIVERSITY MEDICAL COLLEGE,
NEW YORK, *November*, 1909.

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THE ELEMENTS OF THE SCIENCE OF NUTRITION.

CHAPTER I.

INTRODUCTORY.

The earliest scientific observations concerning nutrition were founded upon the commonly noted fact that in spite of the ingestion of large quantities of food, a normal man did not vary greatly in size from year to year. It was understood early in the history of physiology that the weight added by the ingestion of food and drink was lost in the urine, the feces, and the "insensible perspiration." The "insensible perspiration" was partly in evidence when moisture of the warm breath condensed upon a cold plate. By it were meant the usually invisible exhalations from the body, which are now known to be carbon dioxid and water.

Sanctorius[1] made many experiments upon himself and others to determine the amount of insensible perspiration. An old cut shows him sitting in a chair suspended from a large steelyard. As a matter of routine he determined his own weight previous to each meal and then weighted the steelyard so as to counterbalance the additional food he proposed to eat. During the meal when the chair dipped he ended his repast.

In Section I, Aphorism II, Sanctorius gives the following curious advice: "If a physician who has the care of another's health, is acquainted only with the sensible supplies and evacuations, and knows nothing of the waste that is daily made by the insensible perspiration, he will only deceive his patient and never cure him." Aphorism III reads: "He only who knows how

[1] Sanctorius: "De medicina statica aphorismi," Venice, 1614. Translation by John Quincy, M.D., London, 1737.

much and when the body does more or less insensibly perspire, will be able to discern when or what is to be added or taken away either for the recovery or preservation of health."

In 1668 John Mayow, writing in London, stated that the atmosphere contained a constituent which supported combustion as well as animal life.

The modern era of the science of nutrition was opened by Lavoisier. The work of to-day is but the continuation of that done a century and more ago. Lavoisier and La Place made experiments on animal heat and respiration. The great German chemist Liebig received his early training in Paris, residing there in 1822. Liebig's conception of the processes of nutrition fired the genius of Voit to the painstaking researches which laid the foundation of his Munich school. These have been repeated and extended by his pupils, of whom Rubner is chief, and by others the world over. Thus the knowledge often transmitted personally from the master to the pupil, to be in turn elaborated, had its seed in the intellect of Lavoisier. It was he who first discovered the true importance of oxygen gas, to which he gave its present name. He declared that life processes were those of oxidation, with the resulting elimination of heat. He believed that oxygen was the cause of the decomposition of a fluid brought to the lungs, and that hydrogen and carbon were produced in this fluid and then united with oxygen to form water and carbon dioxid. It was he who first made respiration experiments on man, the results of which are briefly described in a letter to Monsieur Terray,[1] written in Paris and dated November 19, 1790. There is no existing record of the apparatus with which Lavoisier worked and early obtained accurate results. The more important conclusions Lavoisier sums up as follows:

1. The quantity of oxygen absorbed by a resting man at a temperature of 26° C. is 1200 *pouces de France*[2] hourly.

[1] Report of the British Association for the Advancement of Science, Edinburgh, 1871, p. 189.

[2] 1 cubic pouce = 0.0198 liters.

2. The quantity of oxygen required at a temperature of 12° C. rises to 1400 *pouces*.
3. During the digestion of food the quantity of oxygen amounts to from 1800 to 1900 *pouces*.
4. During exercise 4000 *pouces* and over may be the quantity of oxygen absorbed.

These remarkable results are in strict accord with the knowledge of our own day. We know more details, but the fundamental fact that the quantity of oxygen absorbed and of carbon dioxid excreted depends primarily on (1) food, (2) work, and (3) temperature, was established by Lavoisier within a few years after his discovery that oxygen supported combustion.

It was, however, quickly noted that if carbon and hydrogen burned in the lungs, the greatest heat would be developed there, a result not in accordance with observation. It was then suggested that the blood dissolved oxygen, and that the production of carbon dioxid and water took place through oxidation within the blood. In 1837 Magnus discovered that the blood did hold large quantities of oxygen and carbon dioxid, which gave apparent support to this theory. Ludwig in his later years believed that the oxidation took place in the blood.[1] Through the critical studies of Liebig, which were published in 1842, it was seen that it was not carbon and hydrogen which burned in the body, but protein, carbohydrates, and fat. Liebig's original theory was that while oxygen caused the combustion of fat and carbohydrates, the breaking down of protein was caused by muscle work. It will be shown later that oxygen is not the cause of the decomposition of materials in the body, but that this decomposition proceeds from unknown causes, and the products involved unite with oxygen. The sum of these chemical changes of materials under the influence of living cells is known as *metabolism*. This process may involve two factors, *catabolism*, or the reduction of higher chemical compounds into lower, and *anabolism*, or the construction of higher substances from lower ones.

[1] Oral statement to the writer.

Liebig was also the father of the modern methods of organic analysis, and with him began the great accumulation of knowledge concerning the chemistry of the carbon compounds, including many products of the animal economy. These discoveries gave the world a knowledge of the constitution of foods, of urine, of feces, and of tissues, which was not possessed by Lavoisier.

Liebig applied to the problems of biology the mental wealth of the newer chemistry which he himself was creating. He knew that protein contained nitrogen, and in 1842 he suggested that the nitrogen in the urine might be made a measure of the protein destruction in the body.[1] Bidder and Schmidt[2] were the first to make systematic experiments upon this subject. They gave meat to dogs and cats and found that almost all the nitrogen contained in the meat was eliminated in the urine and in the feces. They[3] make the following striking statement, which rings quite true to modern thought, concerning protein metabolism: "Almost all the nitrogen of protein and collagen is split from its combination and carries with it enough carbon, hydrogen and oxygen to form urea; the remaining part, containing five-sixths of the total heat value of the protein, undergoes oxidation to carbon dioxid and water which are eliminated in the respiration, the calorifacient function having been fulfilled." The results obtained by Bidder and Schmidt were attacked and were not finally established until proof was afforded by Carl v. Voit,[4] who established the fact that an animal could be brought into what he called nitrogenous equilibrium. In this condition the nitrogen of the protein eaten was equal to the nitrogen eliminated from the body in the urine and feces. Thus Voit[5] fed a dog for fifty-eight days with 29 kilograms of meat

[1] Liebig: "Die organische Chemie in ihrer Anwendung auf Physiologie und Pathologie," 1842.

[2] Bidder and Schmidt: "Die Verdauungssäfte und der Stoffwechsel," 1852, pp. 333 and 339.

[3] Bidder and Schmidt: *Loc. cit.*, p. 387.

[4] Voit: "Physiol. Chem. Untersuchungen," 1857.

[5] Voit: "Zeitschrift fur Biologie," 1866, Bd. ii, p. 35.

containing 986.0 grams of nitrogen, and found 982.8 grams of nitrogen in the excreta of the period. The amount of N in the urine was 943.7 grams, and in the feces 39.1 grams. The difference between the amount of nitrogen ingested and that recovered in the excreta was only three-tenths of one per cent. It therefore seemed extremely probable that the excretory outlet for protein nitrogen was in the urine and in the feces and that other sources of its loss were normally negligible. But in order to establish the fact it was necessary to consider the following questions:

Is the nitrogen of the air built up into organic compounds within the body? Is any protein nitrogen given off as nitrogen gas? As ammonia gas? In the sweat? How much is lost through the growth of the hair, nails, and epidermis?

Lavoisier had said that nitrogen gas had nothing to do with respiration. Regnault and Reiset[1] sometimes found that animals under a bell-jar absorbed nitrogen gas and at other times gave it off. The quantity in both cases was extremely small. Voit explained this by showing that the blood and the tissues always contained nitrogen gas dissolved in proportion to the partial pressure of the gas in the atmosphere. A change of this partial pressure under the bell-jar would change the body's content of dissolved nitrogen and explain Regnault and Reiset's variations.

The experiments of Bachl[2] showed that a rabbit with a tracheal cannula could be made to expire for six hours through Nessler's reagent without the indication of a trace of ammonia in the breath. This has also been shown after making an Eck fistula in a dog,[3] where there is an increase in the amount of ammonia in the blood and in the urine. The lungs are not permeable to ammonia.[4] The ordinary insensible perspiration

[1] Regnault and Reiset: "An. de chimie et phys.," Paris, 1849, Sec. 3, Tome xxvi.

[2] Bachl: "Zeitschrift für Biologie," 1869, Bd. v, p. 61.

[3] Salaskin: "Zeitschrift für physiologische Chemie," 1898, Bd. xxv, p. 463.

[4] Magnus: "Archiv für ex. Pathologie und Pharmakologie," 1902, Bd. xlviii, p. 100.

is not accompanied by any appreciable loss of nitrogenous excreta, although profuse sweating certainly brings out some urea, uric acid, and other nitrogen extractives normally excreted in the urine. The recent experiments of Benedict[1] show that the cutaneous excretions of a resting man may amount to 0.071 gram nitrogen *per day;* of a man at moderate work to 0.13 gram *per hour*, and at hard work for four hours to 0.22 gram *per hour.*

Voit[2] collected the hair and epidermis from a dog for 565 days and found an average daily output of 1.2 grams with 0.18 gram of nitrogen. Moleschott[3] cut the hair and nails of several men once a month. The daily outgrowth of hair was 0.20 gram with 0.029 gram of nitrogen, and of nail substance 0.005 gram with 0.0007 gram of nitrogen. The waste through the human epidermis has not been measured, but it must be very slight. The above sources of error were thus shown to be negligible.

The view that the nitrogen of the urine and feces could be made a measure for the determination of protein metabolism was thus securely established. Urea, the principal nitrogenous end-product derived from protein, was therefore shown to be not an adventitious product, but one normally proportional to the protein destruction. It was known that meat protein in general contained about 16 per cent. of nitrogen, or 1 gram of nitrogen in 6.25 grams of protein. Therefore for every gram of nitrogen found in the excreta, 6.25 grams of protein have been destroyed in the body. It is evident that if protein nitrogen be retained in the body a new construction of body tissue is indicated, whereas if more nitrogen is eliminated than is ingested with the food, a waste of body tissue must take place. The discovery of the method of calculating the protein metabolism led Voit to suggest to Pettenkofer that he construct an apparatus with which the total carbon excretion might be

[1] Benedict: "Journal of Biological Chemistry," 1906, vol. i, p. 263.
[2] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 207.
[3] Moleschott: "Untersuchungen zur Naturlehre," Bd. xii, p. 187.

measured, including that of the respiration as well as that of the urine and the feces. Voit saw that with these data it would be possible to determine just how much of each foodstuff was actually burned in the human body. He has described the delight which he and Pettenkofer experienced when their wonderful machine began to tell its tale of the life processes. The cost of the apparatus, which was considerable, was defrayed by King Maximilian II of Bavaria.

It has been stated that the form of Lavoisier's respiration apparatus is unknown. In 1850 Regnault and Reiset[1] published an account of respiration experiments in which small animals were placed under a bell-jar containing a known quantity of oxygen. The air was kept free from carbon dioxid by pumping it through potassium hydrate. The gaseous exchange between the animal and its environment could be readily ascertained, by determining the amount of carbon dioxid given off and the amount of oxygen absorbed. No attempt was made to determine from what materials the carbonic acid arose. The method of Regnault and Reiset placed the animals in a confined space where poisonous exhalations other than carbon dioxid could collect, and where the atmosphere became saturated with water. Although Regnault and Reiset had no idea of the materials which were oxidized in the animals with which they were experimenting, we find that Bischoff and Voit[2] tried to read such interpretations into the work of Regnault and Reiset. Thus Bischoff and Voit determined the quantity of nitrogen in the urine of a starving dog, which indicated that he had burned in twenty-four hours 218 grams of his own "flesh." The flesh was calculated from the nitrogen elimination on the basis of the knowledge that fresh meat contains 3.4 per cent. of nitrogen. Many of the older experiments were computed on this basis. It was shown that the 218 grams of "flesh" contained 40 grams

[1] Regnault and Reiset: "An. d. Chem. und Pharm.," 1850, Bd. lxxiii, pp. 92, 129, 257.

[2] Bischoff and Voit: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.

of carbon. Bischoff and Voit draw attention to an experiment of Regnault and Reiset, showing that a meat-fed dog of a weight similar to the above gives off 250 grams of carbon and absorbs 900 grams of oxygen in the respiration of twenty-four hours. These figures indicated to Bischoff and Voit that the extra carbon elimination was due to the combustion of fat, and they reached the conclusion that the waste of the body in starvation is dependent on the metabolism of protein and fat. Correct results, however, were attainable only by combining the two methods, so that both the quantity of the nitrogen and carbon of the urine and feces, and the amount of carbon dioxid of the respiration during the same period of time could be ascertained. This was accomplished by the respiration apparatus of Pettenkofer.

The problem to be solved by Pettenkofer included the maintenance of a man in normal surroundings. A small room was therefore constructed which was well ventilated by a current of air. This air entered the chamber freely through an opening in connection with a large room outside and was aspirated from a second opening in the chamber, through a large gas-meter, where its volume was measured (500,000 liters per day). It was evidently impracticable to determine all the carbon dioxid in this large volume of air, but its amount was calculated from the analysis of duplicate samples continually withdrawn from the air leaving the chamber during the time of the experiment. Each sample, as it was pumped out, was made to pass over calcined pumice stone, soaked in sulphuric acid, to remove the water. Next it bubbled through baryta water to remove the carbon dioxid, and then passed through a small gas-meter, where the volume of the sample was measured. After this fashion the amount of carbon dioxid and water coming from the air of the chamber was determined in duplicate. Other duplicate analyses of the air taken outside the ventilator, just before it entered the chamber, were simultaneously made in the same manner as were the analyses of the chamber air itself. Knowing the quantity of carbon dioxid and water entering and leaving the room,

it was easy to calculate how much was derived from the man living in it during the period of experimentation. The experimenters failed to find any other gaseous exhalation from a man, such as ammonia, hydrogen, or methane, which could vitiate their results. Control experiments were made by burning a candle or evaporating a known weight of water within the room. Analysis showed that the carbon dioxid and water so produced were measurable within one per cent. of error.

As an illustration of the practical working of the respiration apparatus the first experiment of Pettenkofer and Voit,[1] which gives the metabolism in a starving man, will be described. The man was allowed a small quantity of Liebig's extract of beef, as the experimenters did not at that time realize the very slight discomfort usually entailed by total abstinence from food. As Liebig's extract has no nutritive value, its effect has been counted out in the following description.

The subject, on entering the living-room of the apparatus, weighed 71.090 kilograms, and he drank during the day 1.0548 liters of water, making a total body weight of 72.1448 kilograms. Twenty-four hours later he weighed 70.160 kilograms and his excreta had amounted to 0.7383 kilogram carbon dioxid, 0.8289 kilogram water from lungs and skin and 1.1975 kilograms of urine. The final body weight plus all the excreta amounted to 72.9247 kilograms. A total body weight of 72.1448 kilograms was converted into a body weight plus excreta amounting to 72.9247. The difference is due to oxygen absorbed. The difference of 0.7799 kilogram represents the amount of oxygen needed to convert the body substance lost into the excretory products obtained. The tabular statement reads:

MAN—STARVATION.

	Kg.		Kg.
Weight at start	71.090	Weight at end	70.160
Water drunk	1.0548	Carbon dioxid	0.7383
		Water in respiration	0.8289
Oxygen absorbed	0.7709	Urine	1.1975
	72.9247		72.9247

[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 478.

The analysis of the urine showed 12.51 grams of nitrogen and 8.25 grams of carbon. A calculation gives the amount of carbon in the respiration as 201.3 grams. If we neglect the feces as being too small in starvation to influence the results, we find that the total carbon elimination for twenty-four hours was 209.55 grams, and the total nitrogen 12.51. In the Liebig extract ingested there were 2.44 grams of carbon and 1.18 grams of nitrogen, which must be deducted from the above in order to obtain the strict loss of carbon and nitrogen from the body during the period of starvation. These values are:

C.....207.11 grams.
N..... 11.33 "

These two figures enabled Pettenkofer and Voit to calculate what substances had burned in the body. As every gram of nitrogen in the excreta is approximately represented by the destruction of 6.25 grams of meat protein, the amount of such protein destroyed by the man was 70.81 grams. It has been found that for every gram of nitrogen present in meat protein there are 3.28 grams of carbon. It is therefore easy to estimate that destruction of protein represented by 11.33 grams of nitrogen involved the elimination of 37.16 grams of carbon. Now, the man eliminated 207.11 grams of total carbon, from which this protein carbon may be deducted, leaving as residue 169.95 grams, which must have originated from a source other than protein. The possible sources are two in number—carbohydrates and fats. In starvation no carbohydrates are ingested and their supply in the form of reserve glycogen is usually counted as being negligible in such experiments as these. The only other source from which the 169.95 grams of extra carbon could have been derived is fat, and as fat contains 76.52 per cent. of carbon, a destruction of 222.1 grams of fat may be calculated. This fasting man therefore destroyed:

Protein..... 70.81 grams.
Fat.....222.1 "

That such metabolism actually did take place was further

indicated by the comparison of the amount of oxygen needed for the destruction of the above constituents, and the amount of oxygen absorption as determined by the experiment.

From the constituents of the protein and fat destroyed, Pettenkofer and Voit deducted the constituents of the urine, which contains part of the C and H belonging to protein. The balance of the carbon and hydrogen was fit for oxidation to carbon dioxid and water. Their calculation may thus be presented:

	Weight in Grams.		
	C	H	O
Composition of the protein burned	37.16	5.8	17.1
Composition of fat burned	169.95	25.7	25.1
Total C, H and O metabolized	207.11	31.5	42.2
Deduct quantity in the urine	8.2	2.0	7.6
Balance available for respiratory CO_2 and H_2O	198.9	29.5	34.6
Oxygen required	530.4	235.7	
Total O required for the formation of CO_2 and H_2O			766.1
Less O in the protein and fat			34.6
Oxygen actually required			731.5
Oxygen absorption as determined			779.9
Difference			48.4

We may reach the same result by using the most modern figures for the oxgyen requirement in the metabolism of the foodstuffs. We now know that to burn 100 grams of meat protein requires 133.43 grams of oxygen, and to burn 100 grams of fat requires 288.5 grams, and to burn 100 grams of starch 118.5 grams. This being true, there are required:

	Oxygen.
For 70.81 grams protein	94.44 g.
For 222.1 " fat	639.55 g.
Total required	733.99 g.
Oxygen absorption as found	779.9 g.
Difference	45.91 g.

Had carbohydrates burned, less oxygen would have been needed, since carbohydrates contain a larger proportion of oxygen than fats. Had the extra 169.95 grams of carbon been

due to the combustion of starch (or glycogen), 382 grams would have burned, requiring 452.7 grams of oxygen instead of 639.5 grams for fat. Pettenkofer and Voit found in the amount of oxygen absorption a confirmation of their belief that the fasting organism supports itself by the combustion of its own protein and fat.

It is apparent from this discussion that *the quantity of oxygen needed in metabolism depends upon the kind of material that burns in the organism*, and also that the relation between the amount of oxygen absorbed and carbon dioxid excreted depends on the same factor. Regnault and Reiset frequently observed that this latter relationship was variable. The ratio of the *volume* of carbon dioxid expired to the *volume of* oxygen inspired during the same time is called the *respiratory quotient.* When carbohydrates burn, the R. Q. is unity; that is, for every hundred volumes of carbon dioxid excreted a hundred volumes of oxygen are absorbed. When protein burns the quotient is $\frac{\text{Vol. } CO_2}{\text{Vol. } O_2} = \frac{78.1}{100}$ or 0.781, and when fat burns the quotient is 0.71. Pettenkofer and Voit calculated that the respiratory quotient in their fasting man was 0.69. This indicated a combustion of fat in the organism.

The further researches of Pettenkofer and Voit were founded on the principles described in the above experiment on a fasting man. If meat and fat were ingested, the carbon and nitrogen excreta were collected, and from these data it was determined how much of each foodstuff was oxidized and whether there was a storage of either in the body or a loss of either from the body. If a mixed diet which included carbohydrates were given, the carbon dioxid elimination increased and the oxygen absorption was such as indicated the combustion of carbohydrates. It was assumed that after deducting the protein carbon from the total carbon eliminated, the balance of extra carbon was derived from the destruction of the carbohydrates in so far as these were ingested; any carbon in excess of this was attributed to fat combustion.

Voit[1] in his necrology of Pettenkofer writes: "Imagine our sensations as the picture of the remarkable processes of the metabolism unrolled before our eyes, and a mass of new facts became known to us! We found that in starvation protein and fat alone were burned, that during work more fat was burned, and that less fat was consumed during rest, especially during sleep; that the carnivorous dog could maintain himself on an exclusive protein diet, and if to such a protein diet fat were added, the fat was almost entirely deposited in the body; that carbohydrates, on the contrary, were burned no matter how much was given, and that they, like the fat of the food, protected the body from fat loss, although more carbohydrates than fat had to be given to effect this purpose; that the metabolism in the body was not proportional to the combustibility of the substances outside the body, but that protein, which burns with difficulty outside, metabolizes with the greatest ease, then carbohydrates, while fat, which readily burns outside, is the most difficultly combustible in the organism."

Since the days of these researches repeated experiments have established the verity of the conclusions drawn. It is interesting to note that among the earliest experiments made were some upon patients in pathological conditions, one suffering from leukemia, another from diabetes.

Besides the influence of foods upon metabolism, the changes brought about by exercise, temperature, and drugs were investigated, not only by the Munich school, but by many other workers. Similar investigations are actively progressing to-day.

Among the important conclusions reached by Voit was that concerning the manner of the metabolism. It has been stated that Liebig believed that fat and carbohydrates were destroyed by oxygen, while protein metabolism took place on account of muscle work.

Voit[2] *showed that muscle work did not increase protein*

[1] Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 1.

[2] Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 169; Bd. ii, 1866, p. 535.

metabolism and that the metabolism was not proportional to the oxygen supply. The oxygen absorption apparently depended upon what metabolized in the cells. Voit believed that the cause of metabolism was unknown, that the process was one of cleavage of the food molecules into simpler products, which could then unite with oxygen. Yeast cells, for example, convert sugar into carbonic acid and alcohol without the intervention of oxygen. In like manner the first products of the decomposition of fat, sugar and protein, are formed in metabolism through unknown causes. Some of these preliminary decomposition substances may unite with oxygen to form carbon dioxid and water, others may be converted into urea, while others under given circumstances may be synthesized to higher compounds. In any case *the absorption of oxygen does not cause metabolism, but rather the amount of the metabolism determines the amount of oxygen to be absorbed.* (See p. 31.)

The statement is frequently met with in the literature of the subject that such and such a disease is the consequence of deficient oxidative power in the tissues. For example, it has recently been stated that alcohol decreases the oxidative power of the liver for uric acid.[1] Such apparent decrease in oxidative power may, however, be due to the fact that the normal oxidizable cleavage products are not formed and therefore no oxidation can take place. It is not due to lack of oxygen that sugar is not oxidized in diabetes, or cystin in cystinuria. There is the normal supply of oxygen present, but the cleavage of these substances into bodies which can unite with oxygen cannot be effected, and hence they cannot be metabolized.

Voit's pupil, Lossen,[2] showed that the carbon dioxid elimination in respiration was independent of the ventilation of the lungs except in so far as forced breathing increased the muscular work and the consequent output of carbon dioxid.

[1] Beebe, S. P.: "American Journal of Physiology," 1904, vol. xii, p. 36.

[2] Lossen: "Zeitschrift für Biologie," 1866, Bd. ii, p. 244; and 1870, Bd. vi, p. 298.

Pflüger,[1] who through different reasoning came to the same conclusion as Voit, devised an experiment in which a rabbit breathed quietly through a cannula, and the oxygen absorption was compared with that of the same animal when rapid artificial ventilation of the lungs with air took place, producing apnea or hyperarterialization of the blood. There was no difference, as is seen from the following table:

	Oxygen Absorbed in C.C. During 15 Minutes.	
	Normal respiration.	Apnea.
Series I.....	201.66	203.88
Series II.....	203.21	210.47

From these experiments it is made sure that the respiration does not cause or regulate metabolism. On the contrary, the metabolism regulates the respiration. *The metabolism of the tissues, through its oxygen requirement and its carbon dioxid production, changes the condition of the blood and thereby regulates the respiration. These distinctions are of fundamental importance.*

Thus far the history of the principles which underlie the exact measurement of the metabolism has been briefly given. By metabolism is meant the chemical changes of materials under the influence of living cells. The first cause of these chemical changes, it has been seen, is unknown, but their results lead to motions of the smallest particles of protoplasm, motions whose totality we call life. Phenomena of life are phenomena of motion, due to liberation of energy in the breaking down of molecules. The motions are principally manifested as heat, mechanical energy, and electric currents. In the organism mechanical energy may be converted into heat, as appears when the work of the heart is converted into heat by the friction of the blood upon the capillaries. Also the current of electricity de-

[1] Pflüger: "Archiv für die ges. Physiologie," 1877, Bd. xiv, p. 1.

veloped at each systole of the heart, or in any other active tissue, is resolved into heat. Thus heat may become a measure of the total activity of the body. It is derived from the total metabolism and must be dependent on it and be a measure of it. Hence the physical activities noted in life are the results of chemical decompositions. Metabolism vivifies the energy potential in chemical compounds.

Lavoisier[1] was the first to recognize that animal heat was derived from the oxidation of the body's substance and to compare animal heat to that produced by a candle. To prove this he burned a known quantity of carbon in an ice-chamber and noted the amount of ice melted. He then calculated the amount of heat produced from a unit of carbon. He and La Place put a guinea-pig in an ice-chamber and noted the amount of ice which melted during ten hours and calculated the heat given off from the animal. They then determined how much carbon dioxid the guinea-pig gave off. The animal yielded 31.82 calories to the ice-chamber, while a calculation from the respiratory analysis showed that 25.408 calories could have been derived by the burning of enough carbon to yield the same amount of carbon dioxid as was eliminated by the animal.

Lavoisier realized several of the errors in his work. For example, the calorimetric determination on the animal was made at a different temperature from that of the respiratory experiment, and Lavoisier knew that cold would raise the carbon dioxid output. Also cold reduced the heat in the animal itself, and, further, the water of respiration was added to that of the melting ice. But Lavoisier concluded that the source of the heat lay in the oxidation of the body.

Crawford, in England, found after burning wax and carbon, or on leaving a live guinea-pig in his water calorimeter, that for every hundred ounces of oxygen used the water was raised the following number of degrees Fahrenheit:

[1] For this literature see Rubner: "Zeitschrift für Biologie," 1893, Bd. xxx, p. 73.

Wax	2.1
Carbon	1.93
Guinea-pig	1.73

Crawford concluded that the heat above produced was due to the transformation of pure air into fixed air (carbon dioxid) and water.

The method of Crawford was in reality one of considerable accuracy. According to the modern computation of Zuntz and Hageman,[1] the following are the values of heat production where one liter of oxygen is used to burn the different food-stuffs in the body:

	Calories.
1 liter of oxygen used in the metabolism of protein yields	4.691
1 " " " " " " " fat "	4.686
1 " " " " " " " starch "	5.046

This table shows that there is a maximum variation of only 7 per cent. in the heat value of a unit of oxygen to the body. Hence the quantity of oxygen absorbed may be utilized as an approximate indicator of heat production (Fig. 10, p. 322).

In 1823 the French Academy offered a prize for the best essay on the subject of animal heat. Depretz and Dulong competed for the prize and it was awarded to the former.

Depretz[2] calculated the amount of heat which would have been liberated in burning the carbon and hydrogen of the metabolism to carbon dioxid and water, and compared this with the amount of heat given off by the animal. The heat as calculated was only 74 to 90 per cent. of what was found, a discrepancy due to faults in the method employed (see p. 42). So Depretz concluded that although the respiration was the principal source of animal heat, food, the motion of the blood, and friction yielded the remainder. Interpretation along the lines of the law of the conservation of energy was obviously beyond the ideas of the time.

Dulong's[3] experiments also led to the same conclusion, that

[1] Zuntz and Hageman: "Stoffwechsel des Pferdes," 1898, p. 245.
[2] Depretz: "Annal. de chim. et de phys.," 1824.
[3] Dulong: *Ibid.*, 1841.

oxidation was insufficient to explain the cause of animal heat, and that there must be other sources of it.

In 1851 R. Mayer laid down the law of the conservation of energy, and Helmholtz demonstrated its general applicability.

Energy cannot arise from nothing, nor can energy disappear into nothing. Where energy is active it must have been elsewhere potential. The sum total of energy remains constant in the universe, but energy may vary in kind. The kinds include mechanical energy, heat, electricity, magnetism, and potential energy. The source of energy on the earth is the sun, excepting the energy of the tides, which is due principally to the moon. The sun unevenly warms the atmosphere, producing winds which drive ships and windmills. The sun's heat lifts the vapor of water into the atmosphere, producing rain, in consequence of which rivers are made to turn machinery. The sunlight acts upon a mixture of hydrogen and chlorin gas, causing them to unite with a loud explosion, and the sun acts upon the green leaf of the plant, causing it to unite carbon dioxid and water, with the production of formic aldehyde, which is built up into sugar, oxygen being given off in the process. The sun's energy required to build up the compound becomes latent or potential in it. Whenever and wherever this sugar is again converted into carbon dioxid and water by oxidation, exactly the same quantity of energy taken from the sun and made potential in the sugar is set free. This sugar in the plant may be further converted into starch, cellulose, fat, and possibly into protein. Plants furnish wood and coal as fuel for the steam-engine. They also furnish the basis of animal food, yielding substances which can build up animal tissues, and which can furnish the energy necessary to maintain those motions in the cells whose aggregate is called life. These motions appear in the body as heat, mechanical work, and electric currents, all of which may be measured as heat. Is this energy completely derived from the metabolism? This question is but the continuation of the old one of Lavoisier in the light of newer science.

Bischoff and Voit[1] in 1860 still calculated the heat value of the metabolism from the heat developed in burning the carbon and hydrogen elements of the metabolism. They recognized, however, that this was a false method, and stated that they should employ the calorific value of fat, starch, and protein, less the urea, since they recognized that urea was capable of undergoing combustion with liberation of heat.

In 1860 Voit[2] took a Thomson calorimeter with him from London to Munich. After Frankland's determination of the heat value of the various foodstuffs and urea Voit[3] prepared a table in 1866 for use in his lectures showing that the metabolism of the fasting man experimented on by Pettenkofer and Voit indicated the production of 2.25 million small calories, while the metabolism on a medium diet was 2.40 million calories.

In 1873 Pettenkofer and Voit[4] calculated that 100 grams of fat were the physiological equivalent of 175 grams of starch. Liebig at that time had suggested that the amount of these substances which could be burned by a man was proportional to the oxygen supply.

Voit, not content with his results, suggested to Schürmann in 1878–79 that he carry on experiments to see in what way carbohydrates and fat were interchangeable in nutrition. Schürmann died before the work was completed and the investigation was continued by Rubner. *The isodynamic law, which showed that the foodstuffs replaced each other in accordance with their heat-producing value, was the result.*

Rubner gives the following, as the quantities of the different foodstuffs which are *isodynamic:*

100 g. fat.
232 g. starch
234 g. cane sugar
243 g. dried meat.

Bischoff and Voit: "Die Gesetze der Ernährung des Fleischfressers," 1860, p. 43.

[2] Voit: "Münchener medizinische Wochenschrift," 1902, Bd. xlix, p. 233.

[3] Voit: *Loc. cit.*

[4] Pettenkofer and Voit: "Zeitschrift für Biologie," 1873, Bd. ix, p. 534.

After Stohmann[1] published his research on the calorific value of foods, urea, etc., Voit commenced the construction of a calorimeter for the measurement of the heat eliminated from the body of a man whose metabolism was simultaneously determined. The results obtained by the use of this machine have never been published.

Rubner[2] in Voit's laboratory during this same period was making a series of valuable calorimetric determinations. The heat value to the body of burning starch and fat were obviously the same as that determined in the calorimeter, since in both cases the same end-products, carbon dioxid and water, resulted. The heat value of protein in the calorimeter was different from its fuel value to the body, since the end-products were different in the two cases. When protein is oxidized in the body, the products of its metabolism are lost in three different ways—through the respiration, urine, and feces. The last two contain latent heat lost to the body, which must be deducted from the heat value of protein determined calorimetrically.

The custom of Stohmann and previous authorities had been to deduct the heat value of urea from the heat value of protein, in order to obtain the actual physiological or fuel value of protein, for the organism. But in the earliest experiments of Pettenkofer and Voit[3] it was recognized that in starvation and after the ingestion of meat, there was a much larger output of carbon in the urine than corresponded to the quantity of urea present. The ratio of nitrogen to carbon was nearly constant in the urine when the conditions of feeding were similar. If urea alone were present, Rubner estimated there would be 0.429 gram of C to 1 of N or an N : C = 1 : 0.429. In starvation the urine contains extractive nitrogen (creatinin, uric acid, etc., having relatively more carbon than urea) which has been de-

[1] Stohmann: "Journal für praktische Chemie," 1885, Bd. xxxi, p. 273, and earlier papers.

[2] Rubner: "Zeitschrift für Biologie," 1885, Bd. xxi, pp. 250 and 337.

[3] Pettenkofer and Voit: *Ibid.*, 1866, Bd. ii, p. 471.

rived from the breaking down of tissue protein, and the ratio is N : C = 1 : 0.728. When meat was ingested the fact that the food contained these extractives made the C : N ratio 0.610. And even after six days' ingestion of meat washed free from extractives the urine of the seventh and eighth days still showed an elimination of carbon other than that due to urea, as was indicated by the ratio 0.532. Therefore, from the metabolism following the ingestion of the proteins of washed meat small amounts of carbon compounds other than urea are eliminated in the urine.

Rubner saw that it was the heat value of the urinary constituents themselves which had to be subtracted from the heat value of protein if the fuel value of protein to the body was to be determined.

The following table shows Rubner's results after burning the dry urine:

CALORIC VALUE OF URINE.

Material Burned.	C : N.	Calories from 1 Gram.	Calorific Value of 1 Gram N.
Urea	0.429	2.523	5.41
Urine after feeding protein	0.532	2.706	5.69
Urine after feeding meat	0.610	2.954	7.46
Urine in starvation	0.728	3.101	8.49

It was not alone necessary to know the heat value of the urine excreted, but also that of the feces. Rubner found that after giving 100 parts of dry muscle containing 5.5 grams of ash there was an elimination of 38.2 grams of the organic part in the urine and 2.7 grams in the feces. The following table represents this division of material in the excreta:

	C.	H.	N.	O.
Composition of 100 parts dry muscle	50.5	7.6	15.4	20.97
Urine contains 38.2 parts	9.63	2.52	15.16	10.9
Feces contain 2.7 parts	1.67	0.25	0.24	0.54
Excreted in urine and feces	11.30	2.77	15.40	11.44
Balance for respiration	39.2	4.8		9.53

Rubner determined the amount of heat produced from 1 gram of ash-free feces after meat ingestion and found it to be 6.127 calories, while 1 gram of ash-free feces after protein (washed meat) ingestion yielded 6.852 calories. The total calorific value of one gram of beef muscle when Rubner burned it in the calorimeter was 5.345 calories. He had now the principal data required to determine its heat value in the body. If from 100 grams of meat 2.6 grams appear as feces having a calorific value of 6.127 calories per gram, then there is here a loss of $6.127 \times 2.7 = 16.83$ calories. If from every 100 grams of meat containing 15.4 grams of nitrogen 15.16 grams of the latter appear in the urine and such urine produced by ingesting meat has a calorific value of 7.46 calories for every gram of nitrogen present, then the energy loss in the urine would be $7.46 \times 15.16 = 112.94$ calories. For dry muscle substance we find therefore:

			Calories.
100 grams muscle			534.5
Waste	Urine 112.94	Total	129.77
	Feces 16.83		
Fuel value of 100 grams of dry muscle			404.73

From this value there must be a slight deduction for the heat present in the protein in its colloidal state but lost on drying, and for the heat of solution necessary to dissolve urea and other urinary constituents. Rubner estimates these as:

Heat for the imbibition of protein	2.688
Heat for solution of urea	1.989
	4.677

Subtracting 4.67 from 404.73 leaves 400.06 calories as the maximum of energy obtainable from 100 grams of the dried solids of meat. The calorimeter shows a heat value of 534.5 calories for the same protein. Of this, 400.06 calories, or 74.9 per cent., are available in the organism, while the remainder, or 25 per cent., goes to waste.

A further calculation shows that every gram of nitrogen in the

urine and feces represents an elimination of heat from protein metabolism equal to 25.98 calories. The heat value of protein under the different physiological conditions was estimated by Rubner after the above fashion, and may thus be tabulated:

CALORIFIC VALUE OF PROTEIN IN NUTRITION.

	Calories Yielded by Metabolism of 100 Grams of Protein in the Body.	Heat Value in Calories of Protein Metabolism Yielding 1 Gm. of N. in the Excreta.
After protein (washed meat) ingestion.....	442.4	26.66
After meat ingestion.....	400.05	25.98
Starvation.....	384.2	24.98

If we know the amount of nitrogen in the excreta we can calculate from these standard figures of Rubner the heat value of the protein metabolism to the body. Rubner found that the heat value of 1 gram of pig's fat (lard) was 9.423 calories. Since fat contains 76.5 per cent. of carbon, it could be calculated that for every gram of carbon eliminated in the respiration, which was the result of fat metabolism, 12.3 calories must have been liberated in the body. These figures enabled Rubner to calculate the amount of heat liberated by the fasting man of Pettenkofer and Voit, whose metabolism we have already discussed. The N excreted was multiplied by 24.98 and the fat carbon by 12.3 which gave the total heat value of the period:

Heat from protein (11.33 Gm. N × 24.98)..... 283 Cal.
Heat from fat (169.95 C × 12.3).....2091 Cal.

Total heat value of the metabolism as calculated...2374 Cal.

Rubner applied such calculations as these to the material at hand in the literature of the time, and discovered that *the heat value of the metabolism of the resting individual is proportional to the area of the surface of his body.* For example, a man in starvation, or on a medium diet, an infant at the breast, and a starving dog, were shown to give off similar quantities of heat

per square meter of surface. To these Rubner subsequently added the results of his researches upon a dwarf. The following tables illustrate this point:

	Yield of Calories per Sq. M. Surface in 24 Hours.
Adult man in starvation	1134
Dog in starvation	1112
Adult man on a medium mixed diet	1189
Breast-fed infant	1221
Dwarf (weight = 6.6 Kg.) medium mixed diet	1231

This law, that the resting animal in starvation or on a medium diet gives off the same quantity of heat per square meter of surface, can be extended so that it applies to all warm-blooded animals. Thus E. Voit[1] has collected data for the following table:

		Calories.	
	Weight in Kg.	Per Kilo.	Per Sq. M. Surface.
Pig	128.0	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Goose	3.5	66.7	967
Fowl	2.0	71.0	947
Mouse	0.018		1188

Rubner from his work on protein considered that the heat value of 1 gram in an average mixed diet might well be placed at 4.1 calories. Of course, such a mixed diet would contain casein (4.4 cal.), the organic substance of meat (4.233 cal.), and vegetable proteins (3.96 cal.). The daily food allowance for animal protein was put at 60 per cent., for vegetable protein at 40 per cent., of the total protein in the mixed dietary. For the value of neutral fats Stohmann's figures for olive oil, animal fat, and butter fat were averaged as follows:

Olive oil	9.384	Calories per Gm.
Animal fat	9.372	" " "
Butter fat	9.179	" " "
Average	9.312	" " "

For the heat value of one gram of fat in a mixed diet Rubner therefore adopted the value 9.3.

[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 120.

The following heat values have been found for carbohydrates:

	Stohmann.	Rubner.
Dextrose	3.692	3.755
Milk sugar	3.877	
Cane sugar	3.959	4.001
Starch	4.116	

Considering the predominating importance of starch in the average diet, Rubner gave the value of 4.1 to the group of carbohydrates in the foods.

Rubner's "standard values" have been widely used throughout the world in determining the average fuel value of a mixed diet. They are:

1 gram of protein.....4.1 calories
1 gram of fat.....9.3 calories
1 gram of carbohydrate.....4.1 calories

Their accuracy has been lately verified by Rubner[1] in the most careful manner.

Atwater and Bryant[2] have sought to modify this standard value and offer the following in substitution:

1 gram of protein.....4.0 calories
1 gram of fat.....8.9 calories
1 gram of carbohydrate.....4.0 calories

Atwater[3] states that these figures are perfectly accurate in computing the average diet (results of 411 experiments). The difference between the two standards probably lies in the fact that Rubner gave comparatively pure foods, while the waste through the feces in Atwater's diets reduced the nutritive availability. Another difference lies in the fact that Atwater[4] uses as a small calorie the amount of heat necessary to raise 1 c. c. of water from a temperature of 19.5° to 20.5° instead of from 0° to 1°, the unit ordinarily employed.

[1] Rubner: "Zeitschrift für Biologie," Festschrift zu Voit, 1901, Bd. xlii, p. 261.

[2] Atwater and Bryant: "Report of the Storrs Agricultural Experiment Station," 1899, p. 110.

[3] Atwater: "Am. Journal of Physiology," 1904, vol. x, "Proceedings of the Am. Physiol. Society," p. xxx.

[4] Atwater and Rosa: U. S. Dept. of Agriculture, Bulletin 63, 1899, p. 55.

Rubner,[1] still working in the Munich laboratory, showed that if the diet were increased from a medium to an abundant amount, the metabolism as indicated by the heat production rose. This *dynamic action* resulting from the excessive ingestion of a foodstuff was greatest with protein, less after fat, and scarcely in evidence after carbohydrates.

Finally Rubner, in his own laboratory at Marburg, evolved an animal calorimeter which could accurately measure the amount of heat a dog produced in twenty-four hours. The dog was placed within the chamber of the calorimeter, and this chamber was attached to a respiration apparatus, so that the metabolism could be calculated according to the method of Pettenkofer and Voit. From the metabolism the heat production could be estimated. The results were a triumphant demonstration of the truth of the law of the conservation of energy. The amount of heat that Rubner[2] calculated should have been derived from the metabolism of the dog during the day spent in the calorimeter was the amount actually given off by the dog to the calorimeter. The metabolism, the cause of the motions of life, was the source of the heat-loss of the body. The results achieved constitute a final verification of the methods of calculating the total metabolism originated by Pettenkofer and Voit.

An epitome of Rubner's experiments is here presented:

COMPARISON OF ESTIMATED HEAT FROM METABOLISM WITH HEAT ACTUALLY PRODUCED.

Food.	Number of Days.	Heat Calculated from Metabolism.	Heat Directly Determined.	Difference in Percentage.
Starvation	5	1296.3	1305.2	—1.42
	2	1091.2	1056.6	
Fat	5	1510.1	1498.3	—0.97
Meat and fat	8	2492.4	2488.0	
	12	3985.4	3958.4	
Meat	6	2249.8	2276.9	—0.42
	7	4780.8	4769.3	+0.43

[1] Rubner: "Sitzungsberichte der bayer. Akademie," 1885, p. 454.

[2] Rubner: "Zeitschrift für Biologie," 1893, Bd. xxx, p. 73.

Following Rubner, Atwater, at one time a pupil of Voit, with the aid of Rosa, the physicist, has constructed a large calorimeter capable of measuring to a nicety the amount of heat given off by a man living in it. This apparatus has confirmed Rubner's experiments and has shown that the energy expended by a man in doing any work, such as bicycle-riding, is exactly equal to the energy set free by metabolism in the body. *Ex nihilo nihil fit.*

This apparatus was the product of many years of labor and its cost was borne by the United States Government. Armsby has completed a similar one for use with cattle, for the Agricultural Station of the State of Pennsylvania. Benedict with great success has extended Atwater's work in the notable Nutrition Laboratory of the Carnegie Institution in Boston. This is housed in a new building splendidly equipped with apparatus for the simultaneous determination of metabolism and heat production. These elaborate and costly devices prove and confirm the general laws of metabolism in the body, through a knowledge of which alone proper systems of nutrition for people under various conditions may be devised. The American Indian when first shown a watch thought it was alive. We, on the other hand, have come to look upon the living organism as a machine. Like the moving locomotive, we burn more if we are to attain a faster speed, or if we are to keep all parts warm in the winter's cold, and a part of the fuel may be wasted as heat. In both cases the motion and the heat are derived from the power in the fuel. The casual observer sees the moving train, but the expert engineer alone knows how and why the wheels go around. The physiologist busies himself answering the similar how and why regarding the mechanism of living things.

Before taking up the details of the work, we may copy the last general pronouncement of Voit[1] upon the subject of metabolism. It reads:

[1] Voit: "Münchener medizinische Wochenschrift," 1902, Bd. xlix, p. 233.

"The unknown causes of metabolism are found in the cells of the organism. The mass of these cells and their power to decompose materials determine the metabolism. It is absolutely proved that protein fed to the cells is the easiest of all the foodstuffs to be destroyed, next carbohydrates, and lastly fat. The metabolism continues in the cells until their power to metabolize is exhausted. All kinds of influences may act upon the cells to modify their ability to metabolize, some increasing it or others decreasing it. To the former category belong muscular work, cold of the environment (in warm-blooded animals), abundant food, and warming the cells. To the latter, cooling the cells, certain poisons, etc.

"In speaking of the power of the cells to metabolize, I have not meant thereby, as may be seen from all my writings, that the cells must always use energy in order to metabolize, but rather I have understood thereby the sum of the unknown causes of the metabolic ability of the cells—as one speaks of the fermentative 'power' of yeast cells.

"The metabolism of the different foodstuffs varies with the quality and quantity of the food. Protein alone may burn, or little protein and much carbohydrates and fat. I have determined the amount of the metabolism of the various foodstuffs under the most varied conditions. All the functions of metabolism are derived from the processes in the cells. In a given condition of the cells, available protein may be used exclusively if enough be furnished them. If the power of the cells to metabolize is not exhausted by the protein furnished, then carbohydrates and fats are destroyed up to the limit of the ability of the cells to do so.

"From this use of materials arise physical results, such as work, heat, and electricity, which we can express in heat units. This is the power derived from metabolism.

"It is possible to approach the subject in the reverse order, that is, to study the energy production (Kraftwechsel) and to draw conclusions regarding the metabolism (Stoffwechsel). It

is perfectly possible to say that the requirement of energy in the body or the production of the heat necessary to cover heat loss, or for energy to do work, are controlling factors of the metabolism; since on cooling the body or on working correspondingly more matter is destroyed. But one must not conclude that the loss of body heat and muscular work are the immediate causes of this increased metabolism. The causes lie in the peculiar conditions of the organism, and muscle work and loss of heat are merely factors acting favorably upon those causes, raising the power of the cells to metabolize. In virtue of this more is destroyed, and secondarily the power to work and increased heat production are determined.

"The requirement for energy cannot possibly be the cause of metabolism, any more than the requirement for gold will put it into one's pocket. Hence the production of energy has a very definite upper limit, which is afforded by the ability of the cells to metabolize. If the cells will metabolize no more, then further increase of work ceases even in the presence of direst necessity; and this is also the case with the heat production, even though it were very necessary, and we were likely to freeze.

"I therefore maintain my 'older' point of view, that of pure metabolism, in order to explain the phenomena of nutrition. I am convinced that it is the right way, and that the clearest and most unifying development will be possible as one investigates what substances are destroyed under different circumstances, such as work, and loss of heat, and how much of the different materials must be fed to maintain the body in condition."

ADDENDUM CONCERNING THE NATURE OF THE FECES.

In the historical introduction just given it has been shown that the nitrogen of the urine and feces can be made a measure for the determination of protein metabolism. It is easy to com-

prehend that urinary constituents, such as urea, uric acid, the purin bases, creatinin, etc., are derived from the metabolism of flesh in the body, whether the flesh be the body's own or that of an animal fed to it. But the intestinal canal where the feces are formed is a long tube open at both ends, through which may pass the nitrogen gas of the air swallowed and indigestible substances such as hair, tacks, etc. In diarrhea the curds of milk, pieces of undigested meat or bread, and large quantities of fat are in evidence. These common observations would seem to justify the popular supposition that normal feces are made up of the undigested residues of the foodstuffs. In truth, however, this is very far from the fact. The feces are chiefly the unabsorbed residues of intestinal excretions.

The collection of the feces for a given period of nutrition is more difficult than the collection of the urine. The urine may be collected every two hours and may fairly represent the protein metabolism of the time, but the feces are normally passed but once a day by a man on a mixed diet, and only once in five days by a dog fed with meat. Furthermore, particles fed to a man are not usually passed in his feces for two or three days. The feces formed during a certain digestive period might therefore leave the body two or three days after the urine was drawn from the bladder. To obtain clear results Voit fed a dog with 60 grams of bones in a preliminary diet eighteen hours before the regular feeding began. These bones yielded a whitish mark in the fecal excretion. All feces subsequent to the mark were attributed to the diet used in the experiment. At the conclusion of the experiment a second diet containing bones was given. The whitish excrement formed from this indicated the end of the feces of the period. For the same purpose Rubner[1] gave milk (2 liters) to a man, the last portion of the milk being taken eighteen hours before the commencement of a period of feeding. The milk feces give a distinct whitish dividing line. A teaspoonful of lampblack may also be readily made use of

[1] Rubner: "Zeitschrift für Biologie," 1879, Bd. xv, p. 119.

in man and in animals. Cremer[1] uses freshly precipitated silicic acid (10 to 25 grams mixed with 40 to 100 grams fat) instead of bones. This gives excellent results, as it avoids the albuminoid nitrogen in the bones, and is of great advantage if the calcium or other ash constituents of the feces are to be determined.

In the fundamental experiments Voit found that a fasting dog weighing 30 kilograms excreted 1.88 grams of dry fecal matter per day, containing 0.15 gram of nitrogen. Evidently these starvation feces are not derived from the food, but must be derived from the matter passed from the body into the intestinal canal. An analogous condition is found in the intestinal tract of the new-born infant. The meconium consists principally of the unabsorbed residues of the bile, of glycocholic, taurocholic, and fellic acids, of cholesterin and lecithin, colored by bilirubin or biliverdin. The absence both of putrefaction and the acid of the gastric juice prevents the breaking up and reabsorption of many of these substances, processes which occur soon after birth. The fasting dog of 30 kilograms, mentioned above, excreted 1.88 grams of dry feces, but a fasting dog of 20.3 kilograms may yield 4.3 grams of dry bile solids in twenty-four hours.[2] The ordinary starvation feces therefore cannot consist of the total of the excretions from the body into the digestive tract, but are rather their unabsorbed remainder.

When meat was given, Bischoff and Voit[3] found that the production of feces was not proportional to the amount of meat. The following table illustrates the average amount of dry feces produced by a dog weighing 35 kilograms after feeding different quantities of meat:

Meat in Grams.	Dry Feces.
500	10.7
1800	11.2
2500	11.93

[1] Cremer: *Ibid.*, 1897, Bd. xxxv, p. 391.

[2] Voit: *Ibid.*, 1894, Bd. xxx, p. 548.

[3] Bischoff and Voit: "Die Ernährung des Fleischfressers," 1860, p. 291.

The feces had the same pitch-black color as starvation feces and were similar to the 2 grams of feces which would have been produced by the same dog had he been starving. No muscle fibers and no protein could be detected. It seemed clear that the meat feces differed from the starvation feces mainly in quantity, and that this quantity was larger because the secretions into the intestines had been stimulated by the passing food.

Fat ingested with the meat in moderate quantities had no influence on the feces. Nor had sugar, unless its fermentation produced diarrhea. Bread somewhat increased the volume of the feces, which contained some undigested starch. Here an irritation of the intestinal canal by the bread produced a larger excretion into the intestine.

The source of the feces was further investigated by Hermann,[1] whose work was later elaborated by Fritz Voit.[2] The latter separated a loop of the intestine about a third of a meter long from the rest of the intestine of a starving dog. Both ends of the loop were tied and the loop remained in the abdomen in connection with its normal nerve and blood supply. The two ends of the remaining portion were reunited. After a few days food could be given and the normal excretion of feces took place. After three weeks the animal was killed. It was found that the isolated loop contained a thick, fecal-looking mass. It was found that the dry solids of this mass contained the same percentage of nitrogen as did the feces passed by the dog during the three weeks of the experiment. It was also calculated that the amount of nitrogen excreted through the wall of the intestinal loop per square meter of its surface was nearly the same per unit of area as the amount of nitrogen in the feces when spread over the surface of the whole of the rest of the intestine. The following table shows this:

[1] Hermann: "Pflüger's Archiv," 1890, Bd. xlvi, p. 93.

[2] F. Voit: "Zeitschrift für Biologie," 1892, Bd. xxix, p. 325.

	Percentage of N in the Dry Substance.		Grams N from 1 Sq. M. in 24 Hours.	
	Feces.	Content of Loop.	Feces.	Content of Loop.
Dog I	5.62	5.32	0.28	0.22
Dog III	5.27	6.88	0.25	0.32

The loop contained fat and fatty acids in greater quantity than is normally found in feces, which may indicate a usual reabsorption of these substances.

Fritz Voit has therefore shown that the excretion of substances from an isolated loop of the intestine produces a mass of a similar constitution and of nitrogen output equal to that in the normal intestine of the same animal through which meat and fat were passing. He therefore concludes that the feces are derived principally from the substances excreted through the wall of the intestine. The nitrogen so excreted is as much to be considered a product of protein metabolism as is the nitrogen of urea. It is regrettable that very little is known regarding the chemistry of these nitrogenous compounds excreted into the intestine.

It has been seen that the feeding of simple foodstuffs, such as meat, fat, and sugar, scarcely influenced the composition of the feces in the dog. In herbivora we pass to another extreme. Here vast amounts of cellulose are eaten, a great part of which is never disintegrated, but even after long retention in the capacious intestinal tract is passed in the feces. After giving an ordinary fodder to a cow, as much nitrogen may be passed in the feces as in the urine. Under such conditions as these, the very voluminous feces evidently do consist largely of the undigested residues of the fodder. Armsby and Fries[1] have shown that only 45 per cent. of the energy contained in hay is of actual use

[1] Armsby and Fries: Bulletin 101, 1908, Bureau of Animal Industry, U. S. Dept. of Agriculture.

in cattle feeding. The waste in the feces reaches 41 per cent., in the urine 7.25, and in methane gas 6.75 per cent. of the total energy content.

Concerning the fecal production in man, it has been found that Cetti[1] excreted 3.8 grams of dry fecal solids per day during a fast of ten days, Breithaupt 2 grams, and a medical student[2] 2.2 grams, less in reality than would a dog of similar size. Benedict[3] states that he was unable to find any evidence of the formation of feces during a seven-day fast in man.

Rieder[4] gave a man a diet containing starch, sugar, and lard from which a cake was baked. The food contained no nitrogen, but the fecal excretion was 0.54, 0.87, and 0.78 gram of nitrogen per day, contrasting with 0.316 gram from Cetti, 0.113 from Breithaupt, and 0.13 from a medical student during fasting. The food, even though it contains no protein, stimulates the fecal production.

Wallace and Salomon[5] have administered 250 grams of cane sugar daily to normal persons and to patients suffering from intestinal diarrhea and have determined the amount of fecal nitrogen during periods of two or three days. The sugar was given in doses of 50 grams dissolved in 300 c.c. of water and flavored with fruits, such as apple and lemon, or with wine. Their results with this diet were as follows:

	N in Feces per Day. Grams.
Normal man	0.539
" "	0.380
Tuberculous ulceration of intestine	3.075
" " " "	4.186
Cancer of intestine	1.74
" " "	1.974
Catarrh of intestine (severe)	1.464
" " " "	1.087

[1] Lehmann, Müller, I. Munk, Senator, Zuntz: "Virchow's Archiv," 1893, Bd. cxxxi, Suppl. Heft.

[2] Johansson, Landergren, Sonden, Tigerstedt: "Skandin. Archiv für Physiologie," 1896, Bd. vii, p. 29.

[3] Benedict: "Influence of Inanition on Metabolism," Carnegie Institution, 1907, p. 345.

[4] Rieder: "Zeitschrift für Biologie," 1884, Bd. xx, p. 378.

[5] Wallace and Salomon: "Medizinische Klinik," 1909, No. 16.

It is evident that the quantity of fecal nitrogen eliminated in intestinal diseases is largely increased.

It has been stated that Voit early noticed the occurrence of starch particles in the feces. A large number of experiments have been made to test the digestibility of the various vegetables and cereals. Rubner[1] fed an able-bodied soldier on 3078 grams of variously cooked potatoes daily and found pieces of potatoes in the feces. He notes that an inhabitant of Ireland will eat 4500 grams of potatoes a day. Friedrich Müller[2] writes that after feeding a large quantity of bread, the feces may have practically the same composition as bread.

The better understanding of this question of the "digestibility" of the carbohydrates has come through the work of Prausnitz[3] and his associates, Moeller and Kermauner. Moeller found that no starch appeared in the feces after feeding well-cooked white, rye, and graham bread, rice or potatoes (even when fed in pieces) or legumes when they were prepared in the form of purée. Legumes not in the form of purée, such as string beans eaten as salad, may resist the action of the digestive juices so that the starch contents of the cell are untouched, and the vegetable cells appear in the feces. These facts explain the appearance of bread in the feces if the bread be badly cooked, or if such a "heavy" bread as pumpernickel be eaten. The imperfectly cooked bread contains starch granules whose coverings are impermeable to the digestive juices, as are also many of those in the unbolted rye of pumpernickel.

Prausnitz finds that if a man be put on a rice diet and then meat be substituted for most of the rice, the composition of the feces does vary with the diet. Such feces he calls *normal feces*. They may contain a negligible quantity of fibers of meat (Kermauner) or of cellulose from the rice.

The feces of six persons placed alternately on meat and rice

[1] Rubner: "Zeitschrift für Biologie," 1879, Bd. xv, p. 146.
[2] Fr. Müller: *Ibid.*, 1884, Bd. xx, p. 375.
[3] Prausnitz: *Ibid.*, 1897, Bd. xxxv, p. 335.

diets yielded normal feces, the percentage composition of the dry solids of which was as follows:

COMPOSITION OF FECES ON DIFFERENT DIETS.

No.	Person.	Principal Food.	N %.	Ether Extract %.	Ash %.
1	H.	Rice	8.83	12.43	15.37
2	H.	Meat	8.75	15.96	14.74
3	M.	Rice	8.37	18.23	11.05
4	M.	Meat	9.16	16.04	12.22
5	W. P.	Rice	8.59	15.89	12.58
6	W. P.	Meat	8.48	17.52	13.13
7	J. Pa.	Rice	8.25		14.47
8	J. Pa.	Meat	8.16		15.20
9	F. Pi.	Rice	8.70		16.09
10	F. Pi.	Meat	9.05		15.14
11	Vegetarian.	Rice	8.78	18.64	12.01
		Average,	8.65	16.39	13.82

It is seen from this that whether the food solids contain 1.5 per cent. N, as in rice, or ten times that, as in meat, the composition of the feces remains uninfluenced. Normal feces result from the eating of any food which is completely digested and absorbed. In all such cases these feces have the same composition and are derived from the intestinal wall. It is therefore not astonishing that a vegetarian of many years' standing produced the same kind of feces when fed on rice as did the other men. The same quality of feces has been obtained after giving good bread.

In this connection it is interesting to note that the heat value of one gram of human feces is very constant whether the person is on a meat diet or a medium mixed diet. Rubner[1] gives the heat value of one gram of organic matter in the feces of a man on a meat diet at 6.403 cal., while on a mixed diet one gram varies between 6.061 and 6.357 cal. The average fuel value of feces is therefore 6.2 calories per gram of dry organic substance, and this changes only when there is a poor utilization of the food.[2]

[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 35.

[2] Rubner: v. Leyden's "Handbuch der Ernährungstherapie," 1903, p. 32.

According to Lhorisch,[1] one may calculate the approximate heat value of feces by reckoning the nitrogen therein as protein nitrogen and multiplying the "protein," "fat" and carbohydrate present, by their usual heat value. The sum of these is said to give a rough estimate of the calorific loss through the feces.

After eating pumpernickel, bad bread, or string beans the waste of undigested residues of these substances may appear in the feces, changing its composition and lowering its percentage of nitrogen content.

In general, Prausnitz finds no difference between the digestibility and absorbability of animal and vegetable foods. Meat, rice, and bread from flour are all digested and absorbed. The ordinary feces indicate whether a given food is a small or a great feces builder, not how much or how little food has been used for the organism.

The value in such foods as cabbage, string beans, cauliflower and the like lies, aside from their flavor, in the fact that their indigestible waste may enhance peristalsis in the intestine. Their food value is small, and if given to those with weak digestions, is dubious. Mendel[2] points out that edible carbohydrate substances, like Iceland moss, agar-agar, Jerusalem artichokes, and inulin, are scarcely attacked by the digestive juices and therefore have little or no direct nutritive function. He[3] also finds that the proteins of mushrooms are not digested in the organism.

[1] Lhorisch: "Zeitschrift für physiologische Chemie," 1904, Bd. xli, p. 308.
[2] Mendel: "Zentralblatt für Stoffwechsel," 1908, Bd. iii, p. 641.
[3] Mendel: "American Journal of Physiology," 1898, vol. i, p. 225.

CHAPTER II.

STARVATION.

Nutrition may be defined as the sum of the processes concerned in the growth, maintenance, and repair of the living body as a whole or of its constituent organs.

An intelligent basis for the understanding of these processes is best acquired by a study of the organism when it is living at the expense of materials stored within itself, as it does in starvation.

Starvation or hunger is the deprivation of an organism of any or all the elements necessary to its nutrition. Thus when carbohydrates and fats only are eaten, protein hunger ensues. If the body is deprived of water or of calcium, thirst or calcium hunger, as the case may be, follows. Complete starvation occurs when all the required elements are inadequate. A fasting dog to whom no food or drink is offered does not undergo starvation in this sense, for the metabolized tissue furnishes enough water for the urine and respiration. There is also no water hunger in a dog when meat is ingested, for the meat contains enough water to dissolve the end-products of its metabolism in the urine. Dogs and cats have no sweat glands in the skin except in the pads of their feet. They therefore are not so susceptible to water hunger as is man, whose body surface is constantly losing moisture.

A true picture of water hunger is presented by Straub,[1] who gave a dog dry meat powder mixed with fat. Under these circumstances water is withdrawn from the tissues to dissolve the urea formed. He found that muscles may lose 20 per cent. of their water content without pathological manifestations, although withdrawal of water somewhat increased the protein metabolism. The experiment could not be carried to the point

[1] Straub: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 537.

of death from thirst, for after a few days the food was regularly vomited, on account of the decreased flow of the digestive secretions and an altered condition of the intestinal canal. The non-absorption of the meat powder threw the body on the resources of its own tissue, and this form of starvation, as has been shown, does not constitute water hunger.

Rubner[1] finds that starving pigeons die of thirst in four to five days, while those allowed only water live twelve days. Water hunger is therefore more quickly fatal than starvation when water is allowed. Under the usual conditions of so-called starvation experiments water is freely allowed, so that water hunger does not enter as a factor into the following discussion.

If water be available, the organism obtains the energy necessary for its continued existence from the destruction of its own store of protein and fat. After a variable length of time the organism succumbs. Exposure to cold greatly hastens the end. What is ordinarily called death from starvation is often really death from exposure.

Succi has fasted several times for thirty days. Dr. Tanner, an American physician, for forty days; and Merlatti in Paris for fifty days. Succi took laudanum in considerable quantity to stay the pain in his stomach, while Merlatti took only water.[2] The effect of fasting on the spirits of the faster varies with the individual. Usually there is a loss of buoyancy of spirit, a decreased desire to work, and a decrease in the actual power of working. Succi, however, was capable of considerable exertion, such as walking and riding, without ill effects. A dog does not manifest the same depression as is seen in man. Dogs may be starved several days before they are run in a hunt. The longest fast on record is that of Kumagawa's[3] dog, which died on the ninety-eighth day. This dog was reduced in weight from 17 to 5.96 kilograms, a loss of 65 per cent.

[1] Rubner: v. Leyden's "Handbuch der Ernährungstherapie," 1903, p. 53.
[2] Luciani: "Das Hungern," 1890, p. 28.
[3] Kumagawa and Miura: "Archiv für Physiologie," 1898, p. 431.

The day to day history of the starving organism must now be considered.

In the first days the amount of protein metabolized depends upon the two factors, the glycogen content of the individual and the quantity of protein ingested before the starvation period. The influence of the first factor was shown by Prausnitz.[1] Fifteen individuals (mostly medical students who were taking a course of instruction in the laboratory) fasted for sixty hours. The first day's urine was collected beginning after twelve hours of fasting. The second day's urine contained in twelve cases more nitrogen than that of the first day of starvation. The lower protein destruction on the first starvation day must have been due to the continued use of sugar from the glycogen supply. It is known that the combustion of sugar considerably reduces the protein metabolism, so the second day and not the first of starvation should be taken as the basis of the fasting protein metabolism.

This influence of glycogen metabolism on that of protein during the first and second days of fasting is beautifully shown in experiments by Benedict[2] (see also p. 65).

INFLUENCE OF GLYCOGEN METABOLISM ON THAT OF PROTEIN IN FASTING. WEIGHTS IN GRAMS.

Individual.	First day.			Second Day.		
	Glycogen Metabolized.		N Eliminated.	Glycogen Metabolized.		N Eliminated.
	Total.	Per Kg.		Total.	Per Kg.	
S. A. B.....	181.6	3.15	5.84	29.7	0.52	11.04
S. A. B.....	135.3	2.31	10.29	18.1	0.31	11.97
S. A. B.....	64.9	1.09	12.24	23.1	0.39	12.45
H. C. K.....	165.6	2.33	9.39	44.7	0.64	14.36
H. R. D.....	32.8	0.59	13.25	41.6	0.76	13.53

It is evident that where there is an abundant glycogen reserve the protein metabolism is reduced by the oxidation of

[1] Prausnitz: "Zeitschrift für Biologie," 1892, Bd. xxix, p. 151.

[2] Bendict: "Metabolism in Inanition," Carnegie Institution of Washington, 1907.

carbohydrates, but where there is little glycogen to draw upon the protein metabolism is high even on the first day of starvation.

The second factor, or the influence of the previous meat ingestion, is especially dominant in dogs. Voit[1] fed a dog weighing 35 kg. with different quantities of meat and noticed the effect on urea elimination during subsequent starvation. The results were as follows:

INFLUENCE OF PREVIOUS DIET ON UREA ELIMINATION IN STARVATION.

	Grams of Urea Excreted During Starvation Following Various Diets.				
	Meat, 2500 G.	Meat, 1800 G.; Fat, 250 G.	Meat, 1500 G.	Meat, 1500 G.	Bread.
Last food day	180.8	130.0	110.8	110.8	24.7
1st fasting day	60.1	37.5	29.7	26.5	19.6
2d " "	24.9	23.3	18.2	18.6	15.6
3d " "	19.1	16.7	17.5	15.7	14.9
4th " "	17.3	14.8	14.9	14.9	13.2
5th " "	12.3	12.6	14.2	14.8	12.7
6th " "	13.3	12.8	13.0	12.8	13.0
7th " "	12.5	12.0	12.1	12.9	...
8th " "	10.1	...	12.9	12.1	...
9th " "	...	...	...	11.9	...
10th " "	...	...	...	11.4	...

It is evident from this that on the sixth day of starvation the urea elimination was the same in all cases, or about thirteen grams of urea per day. He deducted the twelve grams from what he had found for the first days and obtained the grams of urea which were derived from the previous food, as follows:

UREA ELIMINATION IN STARVATION ATTRIBUTABLE TO PREVIOUS DIET.

	Meat, 1500 G.	Meat, 1800 G; Fat, 250 G.	Meat, 1500 G.	Meat. 1500 G.	Bread.
(Last food day)	(168.8)	(118.0)	(98.8)	(98.8)	(12.7)
1st fasting day	48.1	25.5	17.7	14.5	7.6
2d " "	12.9	11.3	6.2	6.6	3.6
3d " "	7.1	4.7	5.5	3.7	2.9
4th " "	5.3	2.8	2.9	2.9	1.2
5th " "	0.3	0.6	2.2	2.8	0.7

[1] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 307.

The amount of extra protein metabolism is seen from the above to be directly dependent on the previous feeding, a common level being reached in all cases on the fifth day of fasting.

These experiments led Voit to differentiate between "circulating protein," which could be absorbed, carried to the tissues, and burned, and "organized protein," the more resistant living protein of the tissues themselves. Voit[1] stated that in metabolism the lifeless protein furnished to the cells by the blood was used in preference to the living organized tissue protein. He quoted Landois's experiments, which show that after producing an artificial plethora through injection of blood, the serum proteins are readily burned and their nitrogen eliminated in the urine, while the red blood-cells containing the organized protein are only slowly destroyed. If serum alone be transfused, its protein is rapidly destroyed.[2]

Even in starvation there is evidence of "circulating protein" as food for the tissues. Thus Miescher showed that the salmon, after entering the Rhine from the sea, virtually starves. Yet the genital organs of both male and female develop greatly, this being at the expense of the muscles, which may lose 55 per cent. of their weight. This protein must have been carried to the various parts of the body in the circulating blood-stream. Miescher finds no indication of any destruction of muscle fibers in this process of emaciation. It is interesting in this connection to note that A. R. Mandel[3] has been able at a pressure of 300 to 350 atmospheres acting on lean meat seventy-two hours old to press out a fluid containing 44 per cent. of the protein present in the fibers, and this without visible change from the normal histological appearance of the muscle.

It seems quite possible that in ordinary starvation protein from muscle and other tissues passes to the blood and is carried to all the organs as circulating protein for the nutrition of their cells.

[1] Voit: "Handbuch der Ernährung," 1882, p. 300.

[2] Forster: "Zeitschrift für Biologie," 1875, Bd. xi, p. 496.

[3] Mandel: Unpublished work from the Munich Clinic of Prof. Fr. Müller.

The great work of Emil Fischer has taught that the essential composition of protein is a structure formed of chains of amino-acids. He has constructed artificial *peptids*, bodies in which two or more amino-acids are united together. For example glycyl-glycin is formed by the union of two molecules of glycocoll with the loss of water, as follows:

$$\begin{matrix} H_2NCH_2COOH \\ H_2NCH_2COOH \\ \text{Glycocoll} \end{matrix} \quad -H_2O \quad = \quad \begin{matrix} H_2NCH_2CO \\ | \\ HNCH_2COOH \\ \text{Glycyl-glycin.} \end{matrix}$$

Fischer has recently hung together eighteen of these radicles in an octodecapeptid containing four leucin and fourteen glycocoll molecules and being l-leucyl-triglycyl-l-leucyl-triglycyl-l-leucyl-octoglycyl-glycin.

$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CHCH_2CHNH_2CO \qquad \text{l-leucyl}$$
$$CH_2NHCO$$
$$CH_2NHCO \qquad \text{tri-glycyl}$$
$$CH_2NHCO$$
$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CHCH_2CH\,NHCO \qquad \text{l-leucyl}$$
$$CH_2NHCO$$
$$CH_2NHCO \qquad \text{tri-glycyl}$$
$$CH_2NHCO$$
$$\begin{matrix} CH_3 \\ CH_3 \end{matrix}\!\!>\!CHCH_2CH\,NHCO \qquad \text{l-leucyl}$$
$$CH_2NHCO$$
$$CH_2NHCO$$
$$CH_2NHCO$$
$$CH_2NHCO \qquad \text{octo-glycyl}$$
$$CH_2NHCO$$
$$CH_2NHCO$$
$$CH_2NHCO$$
$$CH_2NHCO$$
$$CH_2NHCOOH \qquad \text{glycin}$$

$$N = 20.8\ \%$$

This forms a body akin to peptone. The high molecular complex called protein, which constitutes the basis of our being, is, after all, separable into simple chemical compounds. In the larger molecule these amino-acids are chained together, even as in structural framework various iron beams are riveted together. Digestive proteolysis or internal metabolism rends the higher structure of the molecule and leaves its individual supports, the amino-acids, open for further disintegration.[1]

In modern critical consideration of the "circulating protein" it must be borne in mind that the amino-products resulting from protein digestion are probably largely metabolized as such, and are only in part regenerated into protein within the organism (page 188). Since the composition of the blood-plasma is practically the same in starvation as after large digestion of meat (page 78), it is evident that the storage of such regenerated protein must be effected elsewhere than in the blood (page 186).

Another thought is that when tissue protein becomes "circulating protein" in the cited case of the salmon, modern theory would assume its cleavage into amino-acids previous to its regeneration into the tissue protein of the genital organs. Thus Kossel[2] estimates that a salmon weighing 9 kg. deposits at breeding-time in his testicles 27 grams of salmin containing 22.8 grams of arginin. Kossel calculates that metabolism of muscle protein during this time yields ample arginin to form the new salmin.

Although Voit's term "circulating protein," has been frequently misunderstood and differently construed, yet discussion of the subject has served to emphasize the distinction between the behavior of living tissue protein and the lifeless protein (or proteolytic cleavage products) of the nourishing fluid.

This point is furthermore well illustrated by the behavior of gelatin. Voit has demonstrated that although gelatin can

[1] For further details see Plimmer: "The Chemical Constitution of the Proteins," 1908.

[2] Kossel: "Biochemisches Centralblatt," 1906, Bd. v, p. 33.

never be converted into tissue protein nor be retained in the body, its ingestion may in part prevent the combustion of the living protein tissue of the body (page 111).

The amount of protein metabolized by a starving animal in good condition bears quite a constant relationship to the total metabolism involved. Even in different animals this constancy is observed. E. Voit[1] calls attention to the fact that the nitrogen elimination is not dependent on the weight of the animal, since a pig of 115 kilos produces 0.06 gram per kilo, whereas a guinea-pig weighing but 0.6 kilo eliminates 0.65 gram of nitrogen per kilo, or ten times as much. However, a comparison of the percentage of the total energy derived from protein in fasting animals in good condition (*i. e.*, with considerable fat) varies within much narrower limits—between 7.3 and 16.5 per cent. This is shown in the following table:

NITROGEN METABOLISM OF DIFFERENT ANIMALS IN STARVATION.

Animal.	Weight in Kg.	N Elimination.			Percentage of Calories from Protein.
		Total.	Per Kg.	Per Sq. M. Surface.	
Pig	115.0	6.8	0.06	3.2	7.3
Man	63.7	12.6	0.20	6.4	15.6
Dog I	28.6	5.1	0.18	5.2	13.2
Dog II	18.7	3.8	0.20	4.6	10.7
Dog III	7.2	2.2	0.30	5.2	13.5
Rabbit	2.7	1.2	0.46	4.8	16.5
Goose	3.3	0.8	0.23	3.3	7.4
Fowl	2.1	0.7	0.34	4.2	10.0
Guinea-pig	0.6	0.4	0.65	4.2	10.8

It is evident from the above that an average of 90 per cent. of the energy of the fasting metabolism may be supplied by non-protein material. This material is fat (see page 26).

If a fasting organism be kept at the same temperature and under the same conditions as regards the performance of external work, the metabolism is remarkably even from day to day.

[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 188.

Hanriot and Richet[1] showed the even absorption of oxygen and elimination of carbon dioxid during the early days of fasting in man, as is illustrated in this table:

	Liters O_2 per Hour.	Liters CO_2 per Hour.
After 17 hours' fast	17.4	15.3
" 24 " "	16.85	14.15
" 29 " "	16.05	14.3
" 46 " "	16.9	14.35

Later Lehmann and Zuntz[2] made some experiments on the professional faster Cetti. They analyzed his urine and feces, and also obtained two samples of the carbon dioxid eliminated between 10 and 11 A. M., each period of collection lasting from ten to fourteen minutes. In other words, the carbon dioxid output was determined for only twenty to twenty-six minutes daily. From these data the total day's metabolism was calculated. This apparatus as used by Zuntz has the advantage that it can be made in portable form, and may be carried on the back in mountaineering. The person inspires through a mouth-piece provided with a plate of hard rubber which fits between the lips and the teeth. The nostrils are closed with a clamp. The inspired air is drawn through a valve and the expired air is forced through another valve to a gas meter. Arrangements are also provided for the gas analysis of portions of the expired air. Trustworthy results are obtained only when the person under investigation is accustomed to the apparatus. It is of especial value when pronounced temporary variations in the metabolism are to be measured. The method is only approximately correct, but it is more accurate in the even metabolism of starvation than after foods have been ingested. In this method the lower metabolism during the night is not taken into consideration.

The investigation of the metabolism of Cetti during a ten days' fast was as follows.

[1] Hanriot et Richet: "Comptes rendus de l'Academie des Sciences," 1888, Tome cvi, p. 496.

[2] Lehmann and Zuntz: "Arch. f. pathol. Anat.," 1893, vol. cxxxi Suppl., p. 23.

METABOLISM OF CETTI IN STARVATION.

Fasting Days.	Protein.	Fat.	Calories from Protein.	Calories from Fat.	Calories, Total.	Calories per Kilo.
1 to 4.....	85.88	136.72	329.8	1288.2	1618	29.00
5 to 6.....	69.58	131.30	267.3	1237.4	1504	28.38
7 to 8.....	66.30	149.35	254.7	1407.3	1662	31.74
9 to 10.....	67.96	132.38	261.1	1247.4	1508	29.26

A very careful experiment on the metabolism of a fasting medical student twenty-six years old was made by Johansson, Landergren, Sonden, and Tigerstedt.[1] The man fasted five days, doing light work in the respiration apparatus. The metabolism during these days was determined. The excreta in grams were as follows:

METABOLISM OF J. A. IN STARVATION.

Day of Fasting.	N Elimination.			C Elimination.			
	Urine.	Feces.	Total.	Urine.	Feces.	Respiration.	Total.
1.....	12.04	0.13	12.17	8.0	1.1	188.5	197.6
2.....	12.72	0.13	12.84	8.3	1.1	179.4	188.8
3.....	13.48	0.13	13.61	9.9	1.1	172.2	183.2
4.....	13.56	0.13	13.69	10.3	1.1	169.4	180.8
5.....	11.34	0.13	11.47	9.3	1.1	165.8	176.2

The evenness of the carbon and nitrogen elimination is remarkable. From the above figures the following table of the general metabolism is made:

Day of Fasting.	Protein.	Fat.	Calories from Protein.	Calories from Fat.	Calories, Total.
1.....	76.1	206.1	303.5	1916.9	2220.4
2.....	80.3	191.6	320.5	1781.9	2102.4
3.....	85.1	181 2	339.4	1684.7	2024.1
4.....	85.6	177.6	341.4	1651.9	1992.3
5.....	71.7	181.2	286.1	1684.7	1970.8

[1] "Skandin. Archiv für Physiologie," 1896, Bd. vii, p. 54.

Further calculation shows the following relations between the weight of the individual and the calorific production:

Day of Fasting.	Weight in Kilos.	Calories per Kilo.
1	66.99	33.15
2	65.71	32.00
3	64.88	31.20
4	63.99	31.13
5	63.13	31.23

On the fifth day of fasting it is seen that the individual oxidized 71.7 grams of protein, 181.2 grams of fat, and produced 1971 calories, or 31.23 calories per kilogram of body substance. This is presumably the minimum compatible with ordinary life.

Reference has already been made to the notable work of Benedict (see p. 56) entitled "Metabolism in Inanition." Here in seventeen experiments on seven men the metabolism was determined during a fast of two days, and in one instance the starvation period extended over seven days. In these experiments the metabolism of glycogen was for the first time determined. Benedict's fasting individuals were placed in a respiration calorimeter, and in addition to the usual routine the amount of oxygen consumed by them was measured. Knowing the last factor Benedict was able to calculate the amount of glycogen destroyed by deducting from the total oxygen intake the part necessary to oxidize the protein catabolized, and then, in the light of the knowledge of the respiratory quotient (see p. 28), apportioning the remainder of the oxygen to the non-protein carbon dioxid eliminated, in such a way as to indicate the amounts of glycogen and fat destroyed. The heat value of the metabolism thus calculated agreed with the heat as actually measured by the calorimeter in which the man lived within one half of one per cent., whereas if the non-protein carbon of the first day had been reckoned as fat metabolized, as had heretofore been the custom, the discrepancy would have been as high as five per cent. in some instances. This shows the usefulness of a comparison of direct and indirect calorimetry. (See p. 42.)

The results of Benedict's experiment on an individual who fasted for seven days are here reproduced.

METABOLISM OF S. A. B. DURING A SEVEN-DAY FAST.

Day.	Grams.			Calories.				R. Q.	Urine.	
	Protein.	Fat.	Glycogen.	Calculated from Metab.	Directly Determined.	Per Kg.	Per Sq. M.		Ratio N : S.	Ratio N:P_2O_5
1.....	73.4	126.4	64.9	1796	1765	29.7	941	.78	19.6	8.55
2.....	74.7	147.5	23.1	1790	1768	29.9	946	.75	18.6	5.55
3.....	78.1	153.0	5.4	1785	1797	30.8	969	.74	17.38	6.34
4.....	69.8	144.7	25.2	1734	1775	30.8	966	.75	16 11	4.83
5.....	65.2	144.7	8.2	1636	1649	29.0	985	.74	16.26	5.23
6.....	64.4	129.8	21.7	1547	1553	27.5	856	.75	16.27	5.19
7.....	60.8	132.5	18.7	1546	1568	28.0	869	.74	16.28	4.87

This complete and recent experiment reaffirms the principles which have already been enunciated. Benedict found that the pulse-rate showed a distinct tendency to fall. In the above individual the average pulse-rate was 57 on the first fasting day and 51 on the seventh day.

E. Voit[1] gives the following summary of the energy requirements during the early days of starvation in man:

GENERAL TABLE OF STARVATION METABOLISM IN MAN.

Day of Fast.	Weight.	Energy in Calories.			Author.
		Total.	Per Kg.	Per Sq. M. Surface	
1.....	70.6	2359	33.4	1112	Pettenkofer and Voit.
1.....	70.4	2222	31.6	1060	Pettenkofer and Voit.
1 to 5....	64.9	2071	31.9	1042	Tigerstedt.
1.....	59.5	1893	31.8	1012	Zuntz and Lehmann.
1 to 2....	56.0	1773	31.7	985	Zuntz and Lehmann.

To this may be added the average results of the many experiments by Benedict:

[1] Voit, E.: "Zeitschrift für Biologie," 1901, Bd. xli, p. 114.

METABOLISM IN THE EARLY DAYS OF STARVATION.

	1ST DAY.	2D DAY.	3D DAY.	4TH DAY.	5TH DAY.
No. of experiments	18	17	9	5	2
Average cal. per kg.	30.7	31.8	31.0	29.6	28.5
" " " sq. M surface	992	1028	991	938	885

This minimal metabolism requirement of the fasting organism appears remarkably constant in different men. Not only is the total metabolism the same but also the amounts of protein and fat which yield the energy are the same. This is shown by comparing the nitrogen excretion of the different fasters during the first days of fasting. These are as follows:

	CETTI.[1]	BREITHAUPT.[2]	SUCCI.[3]	J.A.[4]	SUCCI.[5]
1	13.55	10.01	13.81	12.17	17.00
2	12.59	9.92	11.03	12.85	11.20
3	13.12	13.29	13.86	13.61	10.55
4	12.39	12.78	12.80	13.69	10.80
5	10.70	10.95	12.84	11.47	11.19
6	10.10	9.88	10.12	.....	11.01

It is thus evident that if the organism has previously been well nourished, the fasting metabolism is remarkably even, about 13 per cent. of the total energy being derived from protein and 87 per cent. from fat.

During prolonged fasting the nitrogen output sinks much below the figures of the earlier days. Thus a woman twenty-four years old averaged 4.15 gm. from the thirteenth to the twenty-fifth day of fasting.[6] A girl nineteen years old whose esophagus had been occluded by drinking sulphuric acid excreted 2.8 grams of nitrogen on the sixteenth day of fasting.[7] An invalid of Tuczec's[8] averaged 4.25 grams of nitrogen between the fifteenth and twenty-first days. Under Luciani's obser-

[1] Munk: "Arch. f. Path., Anat." 1893, Bd. cxxxi, Suppl. p. 25.

[2] Munk: *Ibid.*, p. 68.

[3] Luciani: "Das Hungern," 1890.

[4] Johansson, Landergren, Sonden, and Tigerstedt: "Skandin. Archiv. für Physiol.," 1896, Bd. vii, p. 54.

[5] E. and O. Freund: "Wiener klinische Rundschau," 1901, Bd. xv, p. 91.

[6] Seegen: "Wiener Acad. Sitz. Ber.," Bd. xxxiii, 2 Abth.

[7] Schultzen: "Archiv für Physiologie," 1863, p. 31.

[8] Tuczec: "Arch. für Psychiatrie," Bd. xv, p. 764.

vation, Succi excreted 4.08 grams on the twenty-ninth day, and under E. and O. Freund his nitrogen excretion was 2.82 grams on the twenty-first day. The latter authors say that after this there was a sudden rise in the amount of nitrogen and chlorin in the urine, suggesting the so-called *premortal rise*, which caused them to stop the experiment. About 3 grams of nitrogen in the urine or a daily destruction of 18.75 grams of protein would seem to be the lowest extreme of protein metabolism in the emaciated organism after a prolonged fast. The analyses by E. and O. Freund of Succi's urine during a fast of twenty-one days is the most complete record of the sort. The daily nitrogen excretion is given in grams below:

DAILY NITROGEN EXCRETION OF SUCCI IN STARVATION.

Day.	N.	Day.	N.	Day.	N.
1	17.0	8	9.74	15	5.05
2	11.2	9	10.05	16	4.32
3	10.55	10	7.12	17	5.4
4	10.8	11	6.23	18	3.6
5	11.19	12	6.84	19	5.7
6	11.01	13	5.14	20	3.3
7	8.79	14	4.66	21	2.82

The nitrogen and total sulphur ran together in the urine in the proportion of 17.3 N : 1 S. Munk found the relation $\frac{N}{S}$ to be 14.7 in Breithaupt and 15.1 in Cetti, and Benedict (see p. 65) found 16.27 during the fifth, sixth, and seventh days of starvation. A similar relation between N and S is found in muscle. The sulphur is believed to be derived exclusively from the breaking down of protein.

The nitrogen and total phosphoric acid (P_2O_5) in the urine are not found in the same relation as that in which they exist in meat (7.6 : 1), but there is a greater phosphoric acid excretion. This is also true of the calcium excretion. This greater excretion is due to the metabolism of the bones (Munk). E. and O. Freund found that the $\frac{N}{P_2O_5}$ fell from 5.7 on the first day of Succi's

starvation to between 4.2 and 4.4 during the subsequent periods. Munk found this value to be 4.4 in Cetti during ten days and 5.1 in Breithaupt during six days (consult table on p. 65).

A partial record of the work of E. and O. Freund on Succi is given below. Their analyses of the urine of the first, third, eleventh, and twenty-first days of starvation are in part reproduced.

COMPLETE URINARY ANALYSIS OF SUCCI ON FIRST, THIRD, ELEVENTH, AND TWENTY-FIRST STARVATION DAYS.

	Day of Fasting.			
	1st.	3d.	11th.	21st.
Amt. urine, c.c.	1435	575	378	235
Total N, grams	17.0	10.55	6.32	2.82
Urea N, grams	14.8	9.65	5.64	1.65
Uric acid N	0.29	0.20	0.075	0.046
Purin base N	0.13	0.064	0.042	0.034
Creatinin N	0.134	0.198	0.372	0.025
Ammonia N	0.43	0.144	....	0.10
Total S	3.2	1.3	0.8	....
Total P_2O_5	2.98	2.52	0.41	0.64
Cl	14.9	2.56	1.51	0.7
Ca	0.25	....	0.31	....
Mg	0.33	....	....	....

Examination of the above will show that whereas in the earlier days of the experiment the relationship between urea nitrogen and total nitrogen is the normal of about 85 per cent., during the last days it has fallen to 54 per cent. The balance of the total nitrogen not enumerated above is made up of constituents of unknown character. The Freunds attribute great significance to this distribution of nitrogen in the urine, which was noteworthy between the sixteenth and the twenty-first days. A similar ratio may exist in the urine of a man unaccustomed to exercise who does hard work.[1]

The relative ammonia excretion was apparently the same as normal. The purin bodies ran low. The chlorin excretion almost vanished, so great is the retentive power of the body for its sodium chlorid constituents. Of pathological substances, the urine contained acetone, diacetic acid, urobilin,

[1] Jackson: "Archives italiennes de Biologie," 1901, Tome xxxvi, p. 463.

and dextrose. The dextrose was too small in amount to be quantitatively determined.

Of similar import is the experiment by Cathcart[1] on a professional faster, thirty-one years old, a partial record of which is here presented.

URINARY ANALYSIS OF VICTOR BEAUTÉ ON THE FIRST, THIRD, TWELFTH, AND FOURTEENTH DAYS OF FASTING. WEIGHT IN GRAMS.

	Day of Fasting.			
	1st.	3d.	12th.	14th.
Total N	10.51	13.72	8.77	7.78
Urea N	8.96	12.26	6.62	5.99
Ammonia N	0.40	0.73	1.05	0.73
Uric acid N	0.12	0.06	0.17	0.17
Purin base N	0.029	0.032	0.023	....
Creatinin N	0.42	0.34	0.30	0.24
Creatin N	0.02	0.09	0.09	0.10
Total S	0.614	0.801	0.577	0.536
Total P_2O_5	2.26	2.98	1.55	1.25
Cl	3.2	1.5	0.18	0.24
Ca	....	0.216	....	0.096
Mg	....	0.131	....	0.037
K	....	1.33	....	0.515
Na	....	0.865	....	0.096

In this experiment the ammonia excretion rose to meet an accompanying acidosis. The creatinin excretion gradually fell, whereas the creatin excretion, which is generally considered an index of muscle breakdown (see p. 140), remained quite constant. The relation between the nitrogen and sulphur elimination averaged 15 N : 1 S, or similar to the relation found in muscle, which is 14 N : 1 S. The relatively large potassium excretion and the small sodium excretion indicated respectively the destruction of body tissues which are all rich in potassium salts and the conservation of the body's sodium chlorid supply.

A communication by Brugsch[2] shows that the quantities of β-oxybutyric acid and acetone in the urine become very great in extreme hunger. The experiment was also on Succi, be-

[1] Cathcart: "Biochemische Zeitschrift," 1907, Bd. vi, p. 109.

[2] Brugsch: "Zeitschrift für ex. Pathologie und Therapie," 1905, Bd. i, p. 419.

tween the twenty-third and the thirtieth days of starvation, and showed the following remarkable values:

ACETONURIA IN STARVATION (SUCCI).

Starvation Day.	N in Grams.	β-oxybutyric Acid in Grams.	Acetone in Grams.
23d	5.87	9.24	0.569
24th	6.41	8.43	0.410
25th	6.27	9.85	0.463
26th	6.18	5.28	0.569
27th	6.30	11.62	0.525
28th	4.43	6.99	0.339
29th	4.19	9.15	0.242
30th	8.42	13.60	0.115

The excretion of urea nitrogen ran between 54 and 70 per cent., and the ammonia nitrogen between 15.4 and 35.3 per cent. of the total nitrogen in the urine. The high ammonia neutralized the very considerable acidosis.

Albumin is also of frequent occurrence in the starvation urine of man and animals.

It has already been set forth that the general metabolism is extremely even in fasting, and it may be added that existing evidence shows that the intermediary metabolism has a similar character. Thus Stiles and Lusk[1] found in a fasting dog made diabetic with phlorhizin that whereas the quantity of nitrogen and sugar eliminated slowly fell, the relation between the two (the Dextrose : Nitrogen or D : N ratio) remained constant. This is shown in the following table:

CONSTANT RATIO BETWEEN DEXTROSE PRODUCTION AND N ELIMINATION IN STARVATION.

Period.	D per Hour.	N per Hour.	D : N.
15 hours	2.61	0.735	3.56
6 "	...	0.720	...
3 "	...	0.683	...
12 "	2.39	0.666	3.60
3 "	2.51	0.687	3.65
6 "	...	0.670	...
3 "	2.36	0.643	3.66
11 "	2.32	0.642	3.62

[1] Stiles and Lusk: "American Journal of Physiology," 1903, vol. x, p. 77.

The hour-to-hour sugar production from protein is therefore even and constantly proportional to the protein metabolism.

Parker and Lusk[1] showed that if benzoic acid be administered as lithium benzoate twice a day to a fasting rabbit the animal will combine it with the glycocoll of its metabolism in such quantity that after a preliminary sweeping out of the glycocoll contained in the organism the amount eliminated bears a constant ratio to the total nitrogen elimination of the period. In other words, there is a constant production of glycocoll in the organism which is normally burned, but which in this case is combined with benzoic acid and eliminated in the urine. The formula representing the formation of hippuric acid is as follows:

$$\underset{\text{Benzoic Acid.}}{C_6H_5COOH} + \underset{\text{Glycocoll.}}{NH_2CH_2COOH} = \underset{\text{Hippuric Acid.}}{C_6H_5CO.NHCH_2COOH} + H_2O$$

The results of the experiment indicate a production of 3.98 grams of glycocoll from the metabolism of 100 grams of body protein. The following table begins with the fifth fasting day and the second of benzoate feeding, and is as follows:

CONSTANT RATIO BETWEEN GLYCOCOLL PRODUCTION AND N ELIMINATION IN STARVATION.

	N.	Hippuric Acid.	Ratio Hippuric Acid (or Glycocoll) N : Total N.
5th day of fast	0.990	0.7060	1 : 18.0
6th " " "	1.087	0.6340	1 : 21.6
7th " " "	0.775	0.4944	1 : 19.8
8th " " "	1.148	0.5760	1 : 25.5
9th " " "	0.515	0.3252	1 : 21.8

The average ratio is 1 : 21.5. The glycocoll production seems therefore a normal and constant factor of the protein metabolism. Horse's urine taken at random showed ratios of 1 : 15 and 1 : 17 (see page 133).

[1] Parker and Lusk: "American Journal of Physiology," 1900, vol. iii, p. 478.

The length of life under the condition of starvation generally depends upon the quantity of fat present in the organism at the start. The quantity of fat and protein in an animal at the beginning of starvation or at any time during starvation may be estimated if the day-to-day metabolism be determined and if the whole animal be analyzed for fat and protein at the time of death. The sum of the quantities remaining in the body, and the quantity of waste of previous days, will give the composition of the animal at any definite date during the experiment. E. Voit[1] shows that a rabbit with an original fat content of 7 per cent. lived nineteen days and lost 49 per cent. of his body protein. Another rabbit with an original fat content of only 2.3 per cent. lived but nine days, while the loss of body protein amounted to 35 per cent. At the death of these rabbits the amount of fat found was very small, and the general vitality toward the end was almost exclusively maintained by the combustion of protein. Other animals, however, which lost 22 to 26 per cent. of their protein contained considerable fat at the time of death. E. Voit finds that the greater the amount of fat in the body, the less is the protein metabolism. In animals of equal fat content the relation between the amount of fat and the amount of protein oxidized in the cells in starvation is always the same. When there is no fat, protein may burn exclusively. From this it follows that *the quantity of the protein metabolism in starvation depends upon the amount of fat in the body.*

E. Voit[2] has prepared the following table from an experiment of Schöndorff[3] upon a fasting dog. The quotient $\frac{\text{N content}}{\text{Fat content}}$ gives the ratio between these two components of the organism at the time specified. The ratio $\frac{\text{Energy protein}}{\text{Energy total}}$ gives the percentage of the total energy derived from the protein metabolism. The dog died on the thirty-eighth day of his fast.

[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 545.
[2] E. Voit: *Loc. cit.*, p. 520.
[3] Schöndorff: "Pflüger's Archiv," 1897, Bd. lxvii, p. 430.

PROTEIN METABOLISM IN STARVATION AS INFLUENCED BY THE FAT CONTENT OF THE ANIMAL.

Starvation Day.	Weight in Kg.	N Content / Fat Content.	Excreta N in Grams.	Energy per Sq. Meter Surface.	Energy Protein / Energy Total. Reduced to %
1st to 3d.....	22.4	0.25	7.91	1040	26.5
4th to 13th.....	20.7	0.29	5.38	974	16.2
14th to 15th....	19.7	0.34	5.70	959	18.1
16th to 23d.....	18.7	0.40	5.71	944	19.1
24th to 30th....	17.4	0.57	5.92	919	21.3
31st to 35th	16.2	0.87	6.62	901	25.6
36th.....	15.7	1.19	7.41	889	29.5
37th.....	15.5	1.34	8.41	887	33.8
38th.....	15.2	1.51	8.89	881	36.6

E. Voit finds that the amount of protein metabolism depends so absolutely upon the relation between the amount of fat and protein in the body (the $\frac{\text{N content}}{\text{Fat content}}$) that, knowing this ratio, he says he can estimate the relative protein metabolism. When the ratio rises to 4.84 in the rabbit, then 98.3 per cent. of the total energy may be derived from protein. Had fat still been present in considerable quantity the protein metabolism would have remained low. This is the law which governs the gradual rise in the protein metabolism during starvation, the "pre-mortal rise," it has been termed. The increased combustion of the protein is due to the requirement for energy in an organism which has a constantly decreasing amount of fat upon which to draw.

The actual loss of body weight is greater when protein is the source of energy than when the energy is derived from fat. The reason for this is that if one gram of nitrogen is lost there is a diminution of body weight of 33 grams, which represents just so much tissue waste, and an energy yield of 0.8 calories per gram of "flesh" lost, while the combustion of one gram of fat simply causes the loss of one gram in body weight with an energy yield of 9.3 calories. To obtain equivalent amounts of energy there must therefore be a destruction of eleven and a half times more "flesh" by weight, than when fat is oxidized.

Rubner[1] has maintained a dog for a long period on a diet of fat which was sufficient in amount to cover the energy requirement. The content of body nitrogen fell from 358.3 grams to 166.0 grams, a loss of 53.7 per cent. Rubner finds that during the whole period the daily waste of nitrogen is 0.9 gram per 100 grams contained in the body. This "wear and tear" quota is therefore a function of the intensity of the life processes, being proportional to the amount of protoplasmic material present.

What is the cause of death from starvation? It does not seem to be due to an essential change in the composition of the cells themselves, for no chemical alteration has been detected in them.[2] What, then, is the cause of death? The general argument of E. Voit is as follows: It must be due either to a general failure of all the cells or injury of certain organs which are necessary for life. If the first cause were the true cause, then death would take place when a certain definite percentage of protein loss occurred. This does not happen, since the body loss at the time of death may vary between 20 and 50 per cent. of its original protein content. When the genital organs of the salmon develop at the expense of the liquefying muscle substance brought them by the blood, not a single muscle cell of the fish is killed, even though these lose 55 per cent. of their protein in the process (Miescher). It seems extremely improbable, then, that a much smaller loss of protein in starvation can be the cause of general cellular death. On the other hand, if death be due to the failure of certain organs, especially important to life, the cause is to be found in two factors: Either these organs receive too little nutrition for their proper functioning, or they become so emaciated that they fail in spite of sufficient nutriment. Either the fuel is insufficient or the machine wears out.

[1] Rubner: "Archiv für Hygiene," 1908, Bd. lxvi, p. 49.

[2] Abderhalden, Bergell, and Doerpinghaus: "Zeitschrift für physiologische Chemie," 1904, Bd. xli, p. 153.

The following table gives some answer to this. The general arrangement is in the order of the greater original fat content of the animals:

INFLUENCE OF FAT CONTENT ON PROTEIN METABOLISM AND ON LENGTH OF LIFE IN STARVATION.

Animal.	First Weight, Kg.	Fat in %.		Loss in %.		Days Before Death from Starvation.	Author.
		Start.	End.	Animal.	Body N.		
Dog.....	20.64	19	12	28	22	30	Falk.
Fowl.....	1.95	26	5	42	26	35	Schmanski.
Guinea-pig ...	0.67	16	10	38	26	10	Rubner.
Dog.....	23.05	11	1.7	34	35	38	Schöndorff.
Fowl.....	1.00	9.1	0.7	39	37	12	Kuckein.
Rabbit.....	1.51	7.1	0.4	49	49	19	Rubner.
Rabbit.....	2.53	6.3	0.5	44	49	19	Koll.
Rabbit.....	2.34	6.3	0.5	41	45	19	Rubner.
Fowl.....	1.89	2.7	0.7	34	41	9	Kuckein.
Rabbit.....	2.08	2.3	0.4	35	38	8	Kaufman.
Rabbit.....	2.99	2.3	0.3	32	35	9	Rubner.

In the first three animals a large amount of fat was present at the time of death, and this had prevented a great tissue waste. Abundant food was therefore available for the cells. The cause of death seems, therefore, to be in a reduction of activity in one or more organs important for life.

Again, if the protein loss be kept down by administering protein in quantity insufficient for the heating demands of the organism, the animal is kept living largely on his own fat. Schulz[1] in this way kept two dogs alive for twenty-eight and thirty-eight days, with losses of body nitrogen amounting to only 18 and 7 per cent. of the original quantity. The fat present was only 0.4 to 0.5 per cent. at the end. These dogs certainly suffered from no general loss of cell tissue. E. Voit concludes *that death from starvation is primarily due to loss of substance in organs important to life, but it may also ensue under certain circumstances as a result of deficient nutrition to these organs.*

[1] Schulz: "Pflüger's Archiv," 1899, Bd. lxxvi, p. 379.

Schulz[1] and his pupils let a dog which was fat and well nourished fast for twenty-seven days. On the twenty-fifth day the animal manifested weakness, which, on the twenty-seventh day, appeared to threaten its life. Then for a day 400 c.c. of milk were given to the dog and on four subsequent days 300 grams of meat each day. Although these quantities of food were greatly under the quantity required to maintain the dog without loss of body fat, still the animal recovered its strength, added 7.3 grams of protein nitrogen to its body, and then lived during a second period of sixty-one days of starvation. During this second fasting period the protein metabolism was on a much lower level than during the first period. Schulz notices that when the fasting dog still contains considerable fat, protein in the food is readily retained, even though the content of energy ingested be under the body's needs. When, however, the body fat is nearly exhausted, all the ingested protein and some body protein besides is destroyed to provide for the support of the organism. Schulz concludes that death from starvation is due to auto-intoxication, a condition which was relieved in the fasting experiment mentioned above by the ingestion of meat.

The question of what organs are attacked in starvation has attracted attention. Long ago Voit[2] showed that the muscles of a cat which starved thirteen days lost 30 per cent., while heart, brain, and cord lost 3 per cent. only. In normally nourished animals E. Voit finds that the relative weights of the fat-free organs in animals of the same species are very constant. He[3] uses Kumagawa's[4] results to show what percentage the different organs represent in the fat-free organism of a dog before and after a twenty-four-day fast. The third column represents the percentage loss of the fat-free organ in starvation:

[1] Schulz: "Pflüger's Archiv," 1906, Bd. cxiv, pp. 419 to 462.

[2] Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 353.

[3] E. Voit: *Ibid.*, 1904, Bd. xlvi, p. 195.

[4] Kumagawa: "Aus den Mittheil. d. med. Fakultät der kais. Japan. Univ.," Tokio, Bd. iii, No. 1.

LOSS IN WEIGHT OF DIFFERENT ORGANS DURING STARVATION.

Organ.	Fat-free Animal Contains in Percentage of Weight.		Fresh Fat-free Organ Loses in Percentage Weight during a 24 Days' Fast.
	Well Nourished.	Starvation.	
Skeleton	14.78	21.50	5
Skin	10.30	11.29	28
Muscles	53.77	48.39	42
Brain and Cord	0.94	1.11	22
Eyes	0.11	0.16	3
Heart	0.54	0.69	16
Blood	7.14	5.69	48
Spleen	0.39	0.26	57
Liver	3.98	3.05	50
Pancreas	0.33	0.19	62
Kidney	0.66	0.45	55
Genitals	0.30	0.23	49
Stomach and intestine	5.81	6.02	32
Lungs	0.89	0.97	29

It is apparent that the greatest loss is from the glands and the least from the skeleton. The activity of the glands is greatly reduced in starvation. Luciani found that there was no gastric juice formed during Succi's thirty-day fast, but Langley and Edkins find pepsinogen stored within the cells of the gastric glands. The bile flow continues up to the death of the person, but in diminished quantity, corresponding to the lack of food and the decreasing size of the liver. The writer[1] has noticed a great reduction in the activity of the milk secretion in starving goats, there being a permanent cessation of flow after five days. The percentage of fat increases in the milk, as it does in the blood, liver, and other organs.[2] The fasting organs attract fat from the fat deposits of the body and it is brought to them by the circulating blood. Dextrose is present in the blood up to the last day of life, having its probable origin in a constant production of sugar in protein metabolism. The composition of the plasma of the blood in fasting as regards its protein constituents varies very slightly from the normal. Lewinski[3]

[1] Lusk: Voit's Festschrift, "Zeitschrift für Biologie," 1901, Bd. xlii, p. 41.

[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, Bd. ii, 1, p. 50.

[3] Lewinski: "Pflüger's Archiv," 1903, Bd. c, p. 631.

gives the following comparative analyses of blood-plasma of dogs:

100 C.C. BLOOD-PLASMA CONTAIN OF GRAMS N:

		Total.	Albumin.	Globulin.	Fibrinogen.
Dog I....	Fasting	0.935	0.621	0.257	0.057
	Fed	0.831	0.511	0.240	0.080
Dog II...	Fasting	0.921	0.313	0.544	0.064
	Fed	1.062	0.515	0.423	0.124
Dog III..	Fasting	1.010	0.467	0.450	0.093
	Fed	0.977	0.475	0.402	0.100
	Fasting	1.096	0.554	0.443	0.099
Dog IV...	Fasting	1.052	0.536	0.324	0.192
	Fed	0.877	0.542	0.248	0.087

The only constant change seems to be a slight increase of globulin during fasting. Burckhardt believes this to be due to the passage of globulins from the tissues to the blood. The percentage of hemoglobin and the number of blood-corpuscles are not appreciably affected. It is evident then that the blood in starvation retains the normal composition as regards its nutrient materials, except that it carries fat in increased quantity to the cells. In general the cells are well nourished for the ordinary maintenance of the life functions. Hence the appetite is not an expression of general cellular hunger, but rather the result of a local condition of the gastro-intestinal canal, which stimulates the individual to replenishment.

The glycogen of an animal is greatly reduced during starvation, but after seventy-three days it is not entirely removed.[1] Prausnitz[2] reports that a dog weighing 22 kilograms, after fasting for twelve days and after excreting 287 grams of sugar in the urine as the result of phlorhizin injections, still contained 25 grams of glycogen in his body. The writer[3] has found 0.4 gram of glycogen in the liver of a meat-fed phlorhizinized

[1] Pflüger: "Pflüger's Archiv," 1907, Bd. 119, p. 119.

[2] Prausnitz: "Zeitschrift für Biologie," 1892, Bd. xxix, p. 168.

[3] Reilly, Nolan and Lusk: "American Jour. of Physiol.," 1898, vol. i, p. 397.

dog after eleven days of diabetes and an excretion of over 600 grams of sugar. Exercise will greatly reduce the glycogen content, but the only method of completely freeing the organism of glycogen is by tetanus.[1] Zuntz[2] rid a rabbit of glycogen by strychnin convulsions and then kept the rabbit fasting and under the influence of chloral for 119 hours. During this time 5.25 grams of sugar were excreted in the urine and yet 1.286 grams of glycogen were found in the liver and muscles. This must have gradually arisen from the protein metabolism. The writer[3] made an observation that in a fasting diabetic rabbit tetanus produced an extra elimination of sugar in the urine of 1.1 grams, which undoubtedly was derived from the glycogen content of the organism. (See p. 281.) The quantity eliminated corresponded to the amount found as glycogen by Zuntz as above mentioned.

There now remains a discussion of the influence of work and of change in temperature upon the fasting organism.

Frentzel[4] has shown the effect of external work upon the protein metabolism of fasting dogs. One of the dogs did an amount of work corresponding to 216,937 kilogrammeters in three days. The protein metabolism rose during the working hours and continued high on the last day, which was one of complete rest. Frentzel computes that the nitrogen elimination of the last four days (= 20.7 grams) represents an energy equivalent of 220,300 kilogrammeters. This could not cover the work done by the dog if we add to the measured work that which was done by the heart and respiratory muscles. The protein metabolism of four days is therefore entirely insufficient to cover the work done during three. The source of the energy for the work accomplished must be found in an increased metabolism of fat. The increase in protein metabolism above that

[1] Külz: Ludwig's Festschrift, 1891, p. 119.

[2] Zuntz: Verhandl. der physiol. Ges. zu Berlin, "Arch. für Physiol.," 1893, p. 378.

[3] Lusk: "Zeitschrift für Biologie," 1898, Bd. xxxvi, p. 111.

[4] Frentzel: "Pflüger's Archiv," 1897, Bd. lxviii, p. 212.

of rest was not sufficient to supply 7 per cent. of the energy needed to do the work. The record of the dog's nitrogen metabolism is as follows:

INFLUENCE OF WORK ON THE N METABOLISM OF FASTING DOGS.

Day.	Work or Rest.	Food.	Grams of N Excreted.	
			Per Day.	Per Hour.
1st to 4th.....	Rest.	100 g. lard.	...	.....
5th.....	Rest.	100 g. "	3.13	0.1304
6th.....	Rest.	100 g. "	3.52	0.1467
7th.....	Rest.	Fasting.	3.71	0.1546
8th.....	Rest.	"	3.99	0.1663
9th.....	Work.	"	4.97	*0.3680 †0.1837
10th.....	Work.	"	5.02	*0.2750 †0.1960
11th.....	Work.	"	5.63	*0.2400 †0.2335
12th.....	Rest.	"	5.08	0.2117

* Work. † Rest.

Succi did not show a similar rise of protein metabolism from the effect of work. The eleventh day of his fast he spent in bed. On the twelfth day he rode a horse for an hour and forty minutes, raced for eight minutes with some students, and gave an exhibition of fencing in the evening. During the day he walked 19,900 steps. The urinary nitrogen on the eleventh day (rest) was 7.88 g.; on the twelfth (work), 7.162; and on the days following 3.50, 5.33, 5.14, 5.05. The work done was evidently at the expense of increased metabolism of fat. That this is the case had already been demonstrated by Pettenkofer and Voit.[1] A fasting man at work showed no increase in his protein metabolism, but the quantity of fat burned rose enormously. This is shown by the following comparison of the number of grams of fat burned:

[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 459; C. Voit: *Ibid.*, Bd. xiv, 1878, p. 144.

	Day. 8 A.M. to 8 P.M.	Night. 8 P.M. to 8 A.M.
Rest during day	116 g.	94 g.
Work during 9 hours of day period	312 g.	70 g.

The fat metabolism during the day of work is two-and-a-half times that of the resting day and is presumably the source of the energy for the mechanical work accomplished. During the night following the working day the reduction of fat combustion as compared with the night before is due to more profound sleep.

Another phase of the effect of work is shown in the variation between the day and night metabolism of Tigerstedt's fasting medical student, J. A. The average carbon dioxid excretion in grams for two-hour periods during five days of fasting was as follows. The figures showing the elimination during the hours of sleep are printed in black letters.

	A. M.	P. M.					
Time	10–12	12–2	2–4	4–6	6–8	8–10	10–12
Carbon dioxid (grams)	54.8	57.2	54.1	57.8	59.5	66.4	**46.5**
			A. M.				
Time			12–2	2–4	4–6	6–8	...
Carbon dioxid (grams)			**37.5**	**39.1**	**40.7**	68.6	...

The nitrogen of the urine was also less during sleep than during the waking hours:

Fasting Day.	N in the Urine.	
	Day.	Night (10 P. M. to 10 A. M.).
1st	7.11	4.93
2d	6.87	5.85
3d	6.83	6.65
4th	7.91	5.65
5th	6.36	4.98

Johansson[1] finds that the inequality of night and day metabolism depends on muscular work. Sitting up raises the metab-

[1] Johansson: "Skandinav. Archiv für Physiologie," 1898, Bd. viii, p. 109.

olism, and standing does so still more. Even when one lies in bed, restlessness during the day may increase the metabolism. And when perfect muscular relaxation ensues there may still be influences, such as light on the retina or sounds, which may act reflexly on the organism and slightly increase the metabolism. Johansson illustrates these variations in the following comparisons between night and day excretion of carbon dioxid of starving men, the night CO_2 being figured at 100.

	Night CO_2.	Day CO_2.	Author.
Complete muscular rest.....	100	105	Johansson.
Ordinary rest in bed.....	100	110	Johansson.
Ordinary life (no hard work).....	100	142	Tigerstedt.
" " " " "	100	128	Pettenkofer and Voit.
" " " " "	100	147	Tigerstedt.

Johansson agrees with Tigerstedt that the minimum metabolism of a man in bed is represented by 24 to 25 calories per kilogram daily.

The temperature of the fasting organism is usually normal. Luciani found a normal temperature in Succi during his thirty-day fast. The temperature falls only a few days before death. Sonden and Tigerstedt[1] find that the diurnal variations persist during fasting in their ordinary rhythm. The average temperature of the medical student J. A. during his five-day fast was but 0.16° below his normal temperature when food was allowed him. These diurnal variations are exactly concomitant with the fluctuations of carbon dioxid excretion noted on a previous page. When the carbon dioxid production increases, the temperature rises.

This parallelism may be easily shown by comparing the two factors in the chart (Fig. 2) as given by Sonden and Tigerstedt.[2] Furthermore, the diurnal variations tend to disappear if

[1] Sonden and Tigerstedt: "Skandin. Archiv. für Physiologie," 1895, Bd. vi, p. 136.

[2] Sonden and Tigerstedt: *Loc cit.*, p. 132.

the person be kept in a state of muscular rest, so that the output of energy during the day and the night remains the same. In

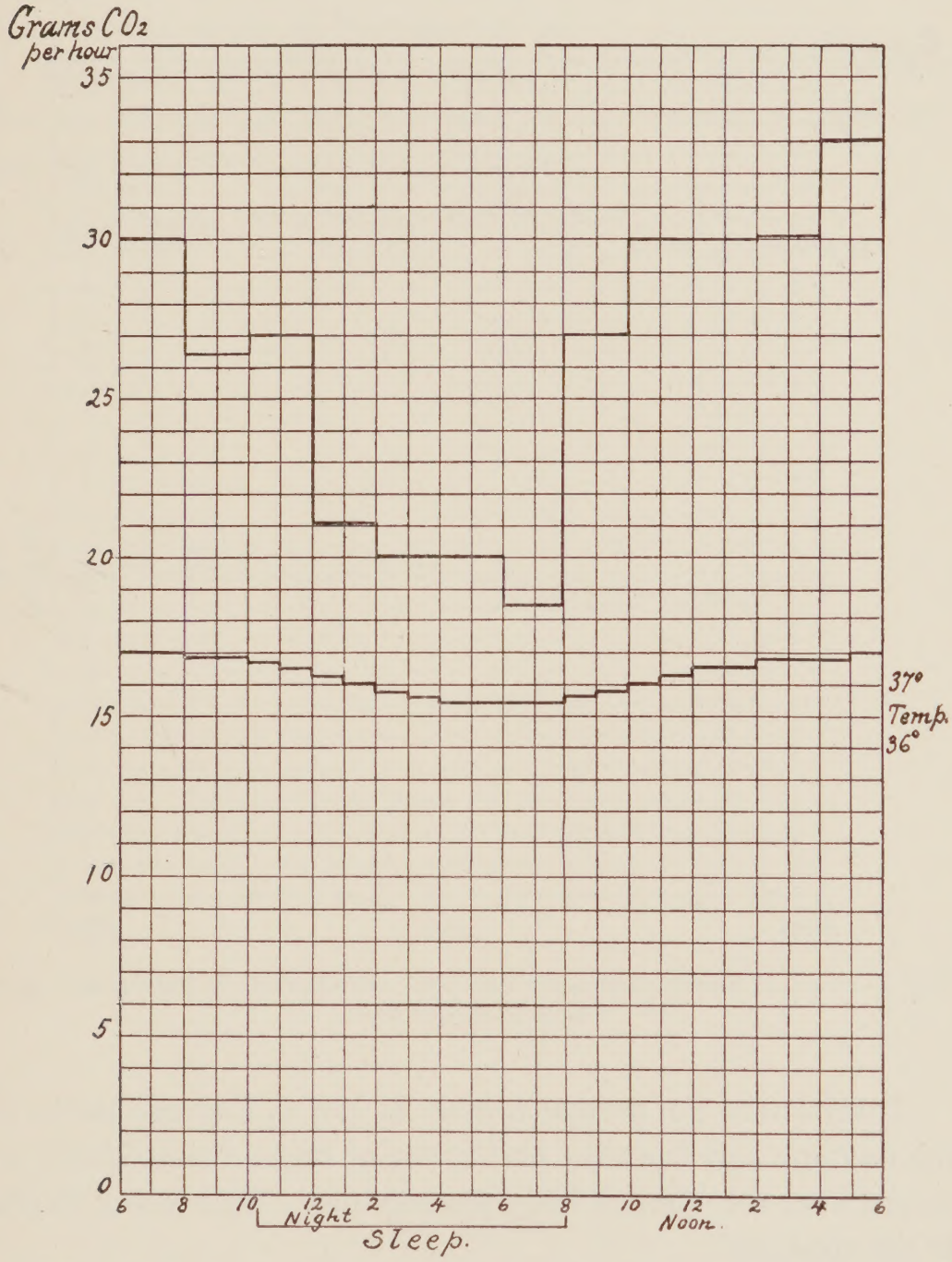


Fig. 1.—Curve of carbon dioxid elimination compared with Jürgensen's curve of normal diurnal temperature variation. This individual led a normal life and partook of his usual nourishment.

this state the temperature may fall 0.6° below the normal on account of the absence of muscle movement. This regularity

of temperature and metabolism is beautifully shown in the following chart of Johansson:[1]

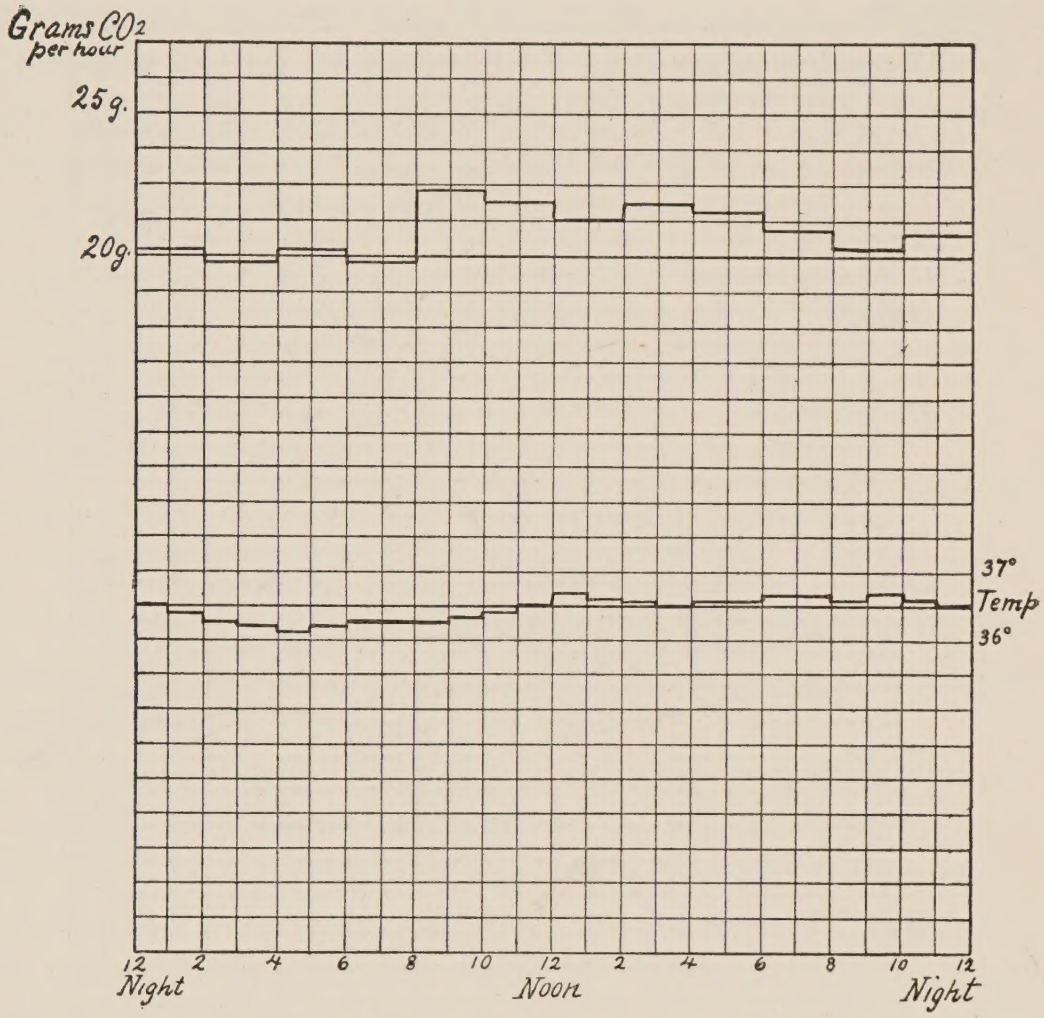


Fig. 2.—Carbon dioxid elimination and body temperature in fasting and complete muscular rest.

Inversion of the normal routine of life, so that one sleeps in the daytime and is awake and active at night, brings about an inversion of the curve of body temperature. This is well shown in the monkey.[2]

Gibson[3] travelled half way round the world in making a trip

[1] Johansson: *Loc. cit.*, p. 142.

[2] Goldbraith and Simpson: Proceedings of the Physiological Society, "Journal of Physiology," 1903, vol. xxx, p. xx.

[3] Gibson: "American Journal of the Medical Sciences," June, 1905.

from New Haven, Connecticut, to Manila, and then returned. He found that the rhythm of daily variation was dependent on the time of the solar day and was independent of the part of the world in which he happened to be.

Benedict,[1] however, was unable to obtain any inversion of the curve of normal body temperature in men who worked during the night and slept during the day.

[1] Benedict: "American Journal of Physiology," 1904, xi, p. 145.

CHAPTER III.

THE REGULATION OF TEMPERATURE.

It has been seen that the temperature of a warm-blooded animal is maintained at the normal throughout a fast. Not only this, but it is maintained at the same level, even though the temperature of the outside environment vary from 0° and lower to 30° to 35°. In cold-blooded animals the temperature of the body is only slightly higher than that of their environment at the time. The metabolism of such animals varies with the temperature. The frog in the mud during the winter at a temperature of 4° C. has quite a different metabolism from that which he enjoys during the summer sunshine as he sits on the river-bank or snaps at passing flies. The curve of his carbon dioxid elimination at various temperatures has been made by E. Voit from the analyses of H. Schultze, and is given below:

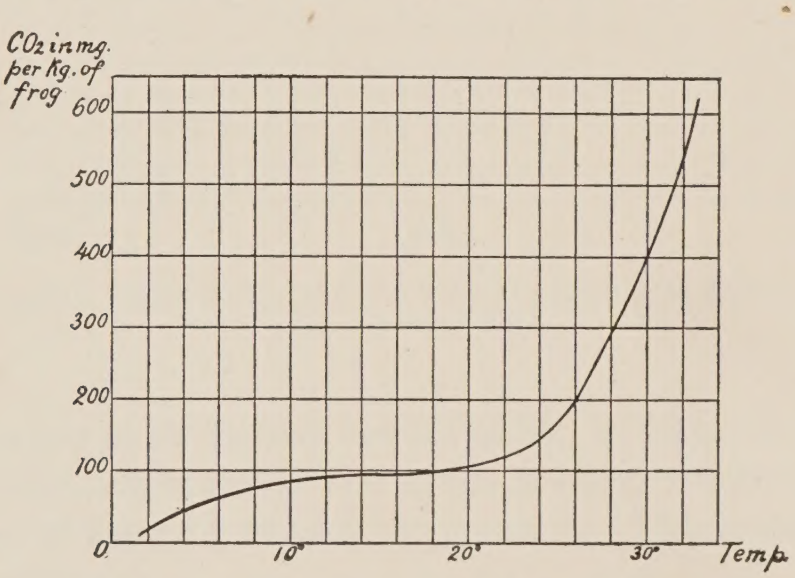


Fig. 3.—CO_2 in milligrams per hour per kg. frog.

A sudden rise in the frog's metabolism commences at about 20°. A temperature of 20° corresponds to that of the bear and marmot during their winter's hibernation, and is a level of compara-

tively low metabolism. This reduction in activity is exemplified by the fact that a cat whose temperature has been artificially reduced to 19° may have but one heart-beat per minute.[1] At the time of hibernation the marmot lives at the expense of fat and retains some glycogen within its muscle tissue. The metabolism may correspond to only one-twentieth the amount of energy used during the period of activity. During the process of waking from the winter sleep the glycogen stored in the muscles is drawn upon.[2]

E. Voit[3] has drawn attention to the fact that the above curve of increasing metabolism with increasing temperature corresponds to the increasing ability of the frog's muscle to contract, and to the increasing effectiveness of enzymotic activity. A high temperature is necessary for the irritability and activity of protoplasm. The warmth of the sunshine increases the irritability of the protoplasm of the tree in the spring, with the resulting development of the foliage. *Warmth, however, is not the cause of the metabolism, but only one of the conditions for it.* In warm-blooded animals the temperature is maintained at a constant level independent of climatic conditions, and this level is a favorable one for the activity of nerve and muscle. It would indeed be inconvenient were the active life of a man dependent upon the temperature of his environment. The essential mechanism for the regulation of the body temperature is through the nerves. The action of cold on the skin may stimulate its peripheral nerve-endings, which are sensitive to cold, and reflexly effect in the organism a greater heat production, and a vaso-constriction of peripheral blood-vessels; the action of heat, on the contrary, effects vasodilatation and production of sweat. It is believed that the cold-blooded progenitors of warm-blooded animals changed their habitat from the sea to the land at a tropical temperature which is at present possessed by their

[1] Simpson and Herring: "Journal of Physiology," 1905, vol. xxxii, p. 305.
[2] Weinland and Riehl: "Zeitschrift für Biologie," 1908, Bd. l, p. 75.
[3] E. Voit: "Sitzungsber. der Ges. für Morph. und Physiol.," 1896, Heft III.

descendants. In the course of development these animals acquired the power to maintain that ancestral temperature, which proved favorable for the activity of their body substance. The nervous mechanism through which this is accomplished is twofold: First, there is an increased production of heat in the presence of external cold (*the chemical regulation of temperature*), and, second, variations in the quantity of blood supplied to the skin modify loss of heat by radiation and conduction and variations in the amount of sweat modify the loss of heat by evaporation of water (these are the factors of the *physical regulation of temperature*). The great importance of these two controlling influences will be seen as the subject develops.

If the body were a mass of cells having the shape of a ball with a constant heat production in its center, it would be easy to calculate its temperature in the different zones of the interior. The loss of heat from the surface would obviously be equal to the heat production, if the temperature of the various zones continued constant.

If two balls of the same material, but of unequal size, were equally warm, the smaller would cool more quickly than the larger on account of the relatively greater exposed surface from which heat could be discharged. The heat elimination would be proportional to the surface exposed.

To determine the surface of geometrically similar solids, and hence of animals of similar shapes, the following formula was used by Meeh,[1] in which S = surface and V = volume:

$$\frac{S}{V^{\frac{2}{3}}} = \frac{S\sqrt[3]{V}}{V}$$

Since animals contain the same materials, one may substitute W = weight for V.

Then the value of $\frac{S\sqrt[3]{W}}{W}$ may be empirically determined for each shape or animal, and this value = k. Hence the formula would read:

$$\frac{S}{W^{\frac{2}{3}}} = k \text{ or } S = k\sqrt[3]{W^2}$$

[1] Meeh: "Zeitschrift für Biologie," 1879, Bd. xv, p. 425.

The value of k or the constant in the relationship of weight to surface in each animal has been given by Rubner as follows:

Man	12.3
Dog	11.2–10.3
Rabbit	12.9–12.0
Rabbit (without ears)	10.8
Calf	10.5
Sheep	12.1
Cat	9.9
Pig	8.7
Guinea-pig	8.5
Fowl	10.4
Rat	9.1
White mouse	11.4

To compute the body surface of a man, for example, the formula $12.3\sqrt[3]{(\text{body-weight})^2}$ would be employed.

The use of the above formula rendered possible the calculation of the heat elimination per unit of area in fasting animals during rest. When these have been previously well fed, there is a surprising uniformity of result. It is Rubner's law that the metabolism is proportional to the superficial area of an animal. In other words, the metabolism varies as the amount of heat loss at the surface, and its variation in accordance with this law is necessary for the maintenance of a constant temperature.

Erwin Voit[1] has calculated the following general table showing the heat production in resting animals of various sizes at medium temperatures of the environment:

		Calories Produced.	
	Weight in Kg.	Per Kilo.	Per Sq. M. Surface.
Horse	441	11.3	948
Pig	128	19.1	1078
Man	64.3	32.1	1042
Dog	15.2	51.5	1039
Rabbit	2.3	75.1	776
Goose	3.5	66.7	969
Fowl	2.0	71.0	943
Mouse[2]	0.018	212.0	1188
Rabbit[2] (without ears)	2.3	75.1	917

The universality of this law of Rubner's is remarkable. Even at a room temperature of 30° where all thermal influence is removed, two guinea-pigs of different sizes will produce heat in

[1] E. Voit: "Zeitschrift für Biologie," 1901, Bd. xli, p. 120.

[2] Rubner: "Energiegesetze," 1902, p. 282.

proportion to their surface. In this case there is a minimum of heat production determined for the resting organism according to the law of superficial area.

When this discovery was first made, the interpretation was offered that the variation in the metabolism of different animals in proportion to the skin area was due to the "chemical regulation" brought about by the specific sensory influences of cold proceeding from a definite area of surface. This explanation fell when Rubner discovered that at a temperature of 30°, under which condition all thermal stimulus to the organism ceased, two guinea-pigs of different sizes still produced heat in proportion to their skin areas. A similar fact was noted by Frank and Voit,[1] who found that the administration of curare, which paralyzes the voluntary muscles, scarcely affected the carbon dioxid output of a dog as compared with what was eliminated during ordinary muscular rest, provided the temperature of the animal was maintained at the normal by keeping him in a warmed chamber. The mass of living cells preserved the same metabolism as before, even though a pathway of heat increase had been cut off through paralysis by curare of the motor nerve-endings in the muscles. Keeping the animal in a warmed chamber was necessary in this case, for Röhrig and Zuntz[2] had shown that curarized animals at the ordinary room temperature lost the power of maintaining their body temperature and that their metabolism decreased accordingly. The removal of the chemical regulation caused a behavior toward external temperature similar to that of cold-blooded animals.

Although the effect of cold on the skin (inducing chemical regulation) is of itself demonstrably insufficient to account for the "law of skin area," Rubner[3] argues that even at 30° C., when the body is losing heat by means of the dilatation of the blood-vessels and the evaporation of water (physical regulation),

[1] Frank and Voit: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 309.
[2] Röhrig and Zuntz: "Pflüger's Archiv," 1871, Bd. iv, p. 57.
[3] Rubner: "Energiegesetze," 1902, p. 174.

the law is still a necessity if the general mechanism for loss of heat in the various animals is the same in all. An infant produces 90 calories per kilogram in twenty-four hours, an adult 32 calories. Were the metabolism of an adult 90 calories per kilogram, the means of heat elimination through his comparatively smaller surface would have to be materially modified if a normal temperature were to be maintained with comfort.

The organism therefore preserves the tropical temperature of its cells at the expense of a metabolism which is proportional to the skin area of the individual.

The loss of heat by an organism is by the following paths:

1. Conduction and radiation.
2. Evaporation of water from lungs and skin.
3. Warming the food ingested.
4. Warming the inspired air (conduction).

The great outlets for heat loss are by conduction and radiation (of which in the dog 97.3 per cent. takes place through the skin and 2.7 per cent. through the lungs[1]) and through the evaporation of water. The losses through warming the food, and through heat of the urine and of solution of urinary constituents, through the feces and the warming of expired carbon dioxid may be ordinarily disregarded.

The pathway for the loss of heat varies with the temperature of the environment. At a low temperature there is little evaporation of water, and at a temperature of 37° there can be no heat loss by radiation and conduction (except by a rise in body temperature) and water evaporation removes the whole of it. In the dog at a high temperature there is spreading out of the limbs to promote heat loss by radiation and conduction, and rapid breathing (polypnea) with extension of the hyperemic tongue to promote evaporation of water. In the horse and in man there is especially an outbreak of sweat, which is not possible in the dog as its skin does not secrete sweat.

It has been seen that Lavoisier noticed that cold increases the metabolism. This has been abundantly confirmed. The

[1] Rubner: "Energiegesetze," 1902, p. 187.

simplest illustration of this action is to be found in fasting animals. Rubner has called this increase of metabolism, and therefore of heat production, the *chemical regulation* of the body temperature. It is the same as burning more coal in the furnace on a cold day in order to maintain the temperature of the house. Voit had previously demonstrated this action in the case of a man (see below).

It will become apparent as the discussion proceeds that a constant basic quantity of energy is necessary to maintain the life-processes of a warm-blooded animal situated in a tropical environment. In this case the *energy* of metabolism is directly concerned in maintaining the vibrant motions of the protoplasm (see p. 360) and heat production is a secondary result. If now the organism be subjected to the influence of a cold environment there is an increased production of *heat* which is directly derived from metabolized substances and the mission of which is to maintain the temperature of the body at the tropical point. It will also be shown in another place how this passive increase in heat production through "chemical regulation," may become unnecessary if instead the needed heat be obtained from other sources, as from the increased heat production incident to muscular work or to food ingestion.

Rubner placed a fasting guinea-pig in a bell-jar which was ventilated so that the carbon dioxid production could be determined. The temperature of the bell-jar could be changed by immersing it in water. The following were the results:

ACTION OF CHEMICAL REGULATION IN THE GUINEA-PIG.

Temp. of Air.	Temp. of Animal.	Grams of CO_2 in 1 Hr. per Kg. Animal.	Percentage Change of CO_2 for Each 1° C. Rise in Temp. of Air.
0.0°	37.0	2.905	—2.33
11.1°	37.2	2.151	
20.8°	37.4	1.766	—1.84
25.7°	37.0	1.540	—2.67
30.3°	37.7	1.317	
34.9°	38.2	1.273	—0.71
40.0°	39.5	1.454	+2.82

It is evident from the table that there was a constant decrease in the metabolism as the air was warmed from 0° to 35° C. The metabolism at 0° was two and a half times that at 30°, an increase as pronounced as is incurred as the result of severe muscular work. The animal at 0° was not observed to move around any more than he did at 30°. Other experiments confirmed Rubner in the view that the *critical temperature*, or the temperature of the minimum metabolism, lay at 33°. At this point temperature had the least influence on total metabolism. When the temperature is raised from 30° there is at first no increase in the metabolism. This is due to the action of the apparatus for the *physical regulation* of body temperature. As the temperature rises the blood-vessels of the skin become dilated and the evaporation of water from the body is promoted. These factors tend to maintain the normal temperature of the organism by physical means. If the temperature of the air be high, so that the physical regulation be not sufficient to cool the body, then a supernormal temperature ensues. Such a febrile temperature raises the metabolism by warming the cells, as is seen in the table of the experiment in which the guinea-pig was exposed to a temperature of 40°. The range of the physical regulation—that is, the period during which external temperature change does not alter metabolism—depends, according to Rubner, on the natural protections which an animal possesses which insure him against heat loss. These are two in number—the hairy covering, and the thickness of the layer of subcutaneous fat.

Rubner has shown that the hair of the black cat, black lamb, rabbit, skunk, raccoon, mink, musk-deer, and sheep is of itself relatively light in weight, but that the fur contains a very large quantity of air. The whole of the fur covering of these animals consists of between 97.3 and 98.8 per cent. of air. The fur therefore really consists of air with between 1.2 and 2.7 per cent. of hair. The slight conductivity of the fur is principally dependent on this layer of stationary air. If an animal be covered

with a fur containing this stagnant air, he will be better protected from loss of heat than if he had none, and also less susceptible to the influence of cold upon the surface of his skin. This protective covering therefore extends the range of the physical regulation.

Rubner[1] gives the following experiment showing the influence of temperature on a small fasting dog with long hair:

ACTION OF CHEMICAL REGULATION IN THE DOG.

Day.	N in Urine.	N in Feces.	Total N.	C of Respiration.	C of Urine.	Total C.	C from Fat.	Cal. from Protein.	Cal. from Fat.	Total Calories.	Temperature.
1st.....	1.80	0.06	1.86	20.0	1.1	21.0	14.9	46.5	183.6	230.1	20.0°
2d.....	1.56	0.06	1.62	22.4	1.0	23.4	18.0	40.4	224.6	264.6	15.2°
3d.....	1.52	0.06	1.58	28.2	1.0	29.1	23.9	39.5	294.7	334.2	7.6°
4th.....	1.56	0.06	1.62	18.9	1.0	19.9	14.5	40.5	179.0	219.5	30.0°
5th.....	1.42	0.06	1.48	17.3	0.9	18.2	13.7	37.0	169.3	206.3	25.2°

One observation was made in this experiment on the dog which was not possible in the case of the guinea-pig, and that concerned the nitrogen excretion. The nitrogen excretion for twenty-four hours is not increased by exposing the dog to a temperature of 7.6°. The increased metabolism is entirely at the expense of fat. We have seen that this may also be true of work which may be accomplished at the expense of fat without raising the protein metabolism.

Reduced to terms of calories produced per kilogram of dog, the following results are obtained:

Temperature.	Calories per Kilo.
7.6°	86.4
15.0°	63.0
20.0°	55.9
25.0°	54.2
30.0°	56.2
35.0°	68.5

[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 105.

A temperature of 20° was readily borne by this dog without any increase of his metabolism. The period of unchanging metabolism extended over at least ten degrees between 20° and 30°, during which time the physical regulation alone sufficed to maintain evenly the body's temperature. At 35° a decided increase of heat production set in, on account of the warming of the cells through insufficient heat loss. That the range of the physical regulation of the temperature of this small dog was due to his long hair is shown by the change in his metabolism after shaving him. Rubner shows this in the following table:

Temperature.	Calories per Kilo.	
	Normal Coat of Hair.	Shaved.
20°	55.9	82.3
25°	54.2	61.2
30°	56.2	52.0

It is clearly seen that this dog lost his power of physical regulation between 20° and 30° as soon as he lost his covering of hair. His metabolism became like that of the guinea-pig, increasing with a reduction of temperature from 30° downward, an illustration of chemical regulation.

E. Voit[1] shows that the metabolism of a pigeon may be doubled after removing its feathers.

Babak[2] finds that if rabbits are shaved and varnished with starch paste their metabolism rises 140 per cent., which increase maintains their body temperature at the normal for several weeks, although the room temperature be between 15° and 20°.

To determine the influence of the second factor, that of the protecting layer of fat, Rubner[3] investigated the influence of

[1] Voit: "Sitzungsber. der Ges. für Morph. u. Physiol.," 1904. Bd. xix, p. 39.

[2] Babak: "Pflüger's Archiv," 1905, Bd. cviii, p. 389.

[3] Rubner: *Ibid.*, 1902, p. 137.

temperature on the metabolism of a fasting short-haired dog, at a time when he was emaciated, and compared it with the fasting metabolism after the same dog had been fattened. The results were as follows:

Dog (Thin).		Same Dog (Fat).	
Temperature.	Cal. per Kilo.	Temperature.	Cal. per Kilo
5.1°	121.3	7.3°	120.5
14.4°	100.9	15.5°	83.0
23.3°	70.7	22.0°	67.0
30.6°	62.0	31.0°	64.5

It appears from the above that the metabolism of the dog was the same at a low temperature in both cases, but that the minimum metabolism was almost reached at a temperature of 22° when the dog had a protective covering of fat, which was not the case when he was thin. The presence of adipose tissue, therefore, acts in the same way as does a warm fur to extend the range of the physical regulation, and to delay the onset of the chemical regulation of body temperature.

The physical regulation may be increased by certain voluntary acts, such as are observed when a dog exposed to cold lies down and curls himself up in such a way as to offer as small an exposed surface as possible. The contrast to this is offered when on a hot day the dog lies on his back and extends his limbs so as to promote the loss of heat.

Rubner[1] compared the fasting metabolism of a resting dog exposed to air at about 18° with that of the same dog quietly resting suspended in a net, by which means his surface was more exposed to the influence of cold. The results were as follows:

	Day of Starvation.	Cal. from Protein.	Cal. from Fat.	Total.	Temp.
Resting	2	33.79	430.91	464.7	17.5°
Resting in net	3	33.79	581.50	615.2	18.2°

Rubner[2] also cites an important modification of metabolism through a variation in the humidity of the atmosphere.

[1] Rubner: "Energiegesetze," 1902, p. 184.

[2] Rubner: *Ibid.*, 1902, p. 188.

At a medium temperature during fasting (as well as on a medium diet) the metabolism of a dog was practically unaffected by an increase of humidity in the air, as appears below:

Temperature 20.2°	Cal. in 24 Hours.	Humidity in Per Cent.
Dry day	258.4	34
Humid day	256.6	69
More on dry day	1.8	

However, on a liberal diet the metabolism increases on a damp day even at a medium temperature, as for example:

Temperature 20.2°	Cal. in 24 Hours.	Humidity in Per Cent.
Very dry day	249.4	13
Humid day	261.9	66
More on humid day	12.5	

The increase is 5 per cent.

On a very hot day (on a moderate fat diet) the dog's metabolism is increased by the presence of moisture in the atmosphere.

Temperature 35°.

Calories per Kg.	Humidity in Per Cent.
69.28	9.1
73.54	30.0

Under these circumstances the metabolism rose 6.1 per cent. in the more humid air. There was probably an overwarming of the cells, on account of the difficulty of heat loss by evaporation of water. A cold, damp environment of 0° to 5° temperature also favors an increased metabolism. Rubner attributes this action of humidity to the increased conductivity of a hair covering containing moisture, and says that this loss may be partially balanced by a decreased evaporation of water from the lungs.

The metabolism and the manner of heat loss may therefore be variously affected by the condition of the atmosphere as regards moisture.

On days of ordinary dryness Rubner[1] calculates the follow-

[1] Rubner: "Energiegesetze," 1902, p. 189.

ing division of the heat loss in a starving dog under the influence of different temperatures:

INFLUENCE OF TEMPERATURE ON MANNER OF HEAT LOSS.

Temperature.	Calories Lost by Conduction and Radiation.	Calories Lost by Evaporation of Water.	Total Calories of Metabolism.	Humidity in per Cent.
7°.....	78.5	7.9	86.4	24
15°.....	55.3	7.7	63.0	34
20°.....	45.3	10.6	55.9	29
25°.....	41.0	13.2	54.2	19
30°.....	33.2	23.0	56.2	14

It is clear that at 7° only a little heat is lost by the evaporation of water and the greater part by conduction and radiation. As the surrounding air becomes warmer the power to lose heat by radiation and conduction diminishes and the loss through the evaporation of water increases.

Rubner has charted this experiment after making allowances[1] for the varying moisture conditions. The chart is reproduced on p. 99. The chart epitomizes the method of heat loss in a starving dog under the influence of varying temperatures.

The discussion of the metabolism has given a foundation for the understanding of the basic requirement of an organism. The minimum requirement for energy is seen to be present when the fasting organism is surrounded by an atmosphere having a temperature of 30° to 35°. This may be called the *basal requirement*, the minimum of energy compatible with cell life. This basal requirement is modified by temperature, by food, and by work, and it is an important factor to keep in mind (see p. 210).

The principles laid down here regarding the lower animals apply equally to man. He too may come under the influence of chemical regulation, although he constantly endeavors to maintain the surface of his skin at a tropical temperature through the use of clothes. His heat loss may, like the dog's, be more

[1] Rubner: "Archiv für Hygiene," 1891, Bd. xi, p. 208.

difficult if he be covered with a thick layer of fat. And his metabolism is also influenced by atmospheric conditions of moisture, wind, and temperature.

One of the earliest demonstrations of the action of chemical regulation was afforded by Voit, who placed a fasting man

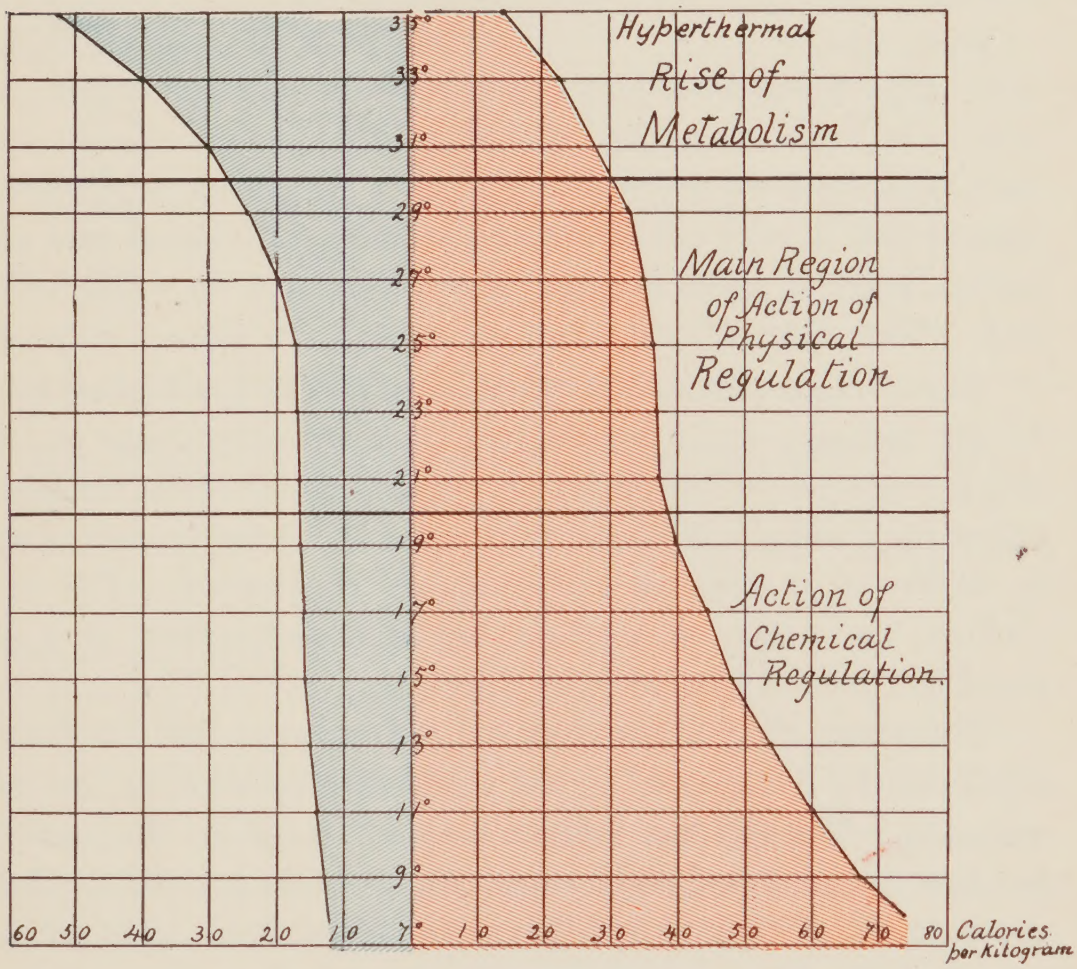


Fig. 4.—Rubner's chart showing the manner of heat loss at different room temperatures in the dog. *Blue*, Heat loss in calories through evaporation of water. *Red*, Heat loss in calories through radiation and conduction.

The distance between opposite points of the curved line represents the total metabolism at a particular temperature.

weighing 70 kilograms in the Pettenkofer-Voit respiration apparatus and determined the carbon dioxid and nitrogen output for six hours. The person accustomed himself to the given temperature by staying under its influence for some time previous to the commencement of the experiment. In the cold experiments the ventilating air was derived from the winter atmos-

phere. For the warm periods the air was artificially heated. The subject of the experiment wore clothing which was comfortable in the usual warm atmosphere of the laboratory. Voit[1] gives the following results:

EFFECT OF TEMPERATURE ON THE METABOLISM OF A FASTING MAN. SIX-HOUR PERIODS.

Temperature.	CO_2 Excreted in G.	N in Urine in G.
4.4°	210.7	4.23
6.5°	206.0	4.05
9.0°	192.0	4.20
14.3°	155.1	3.81
16.2°	158.3	4.00
23.7°	164.8	3.40
24.2°	166.5	3.34
26.7°	160.0	3.97
30.0°	170.6	...

The nitrogen elimination remains unaffected by temperature. At the ordinary room temperature there scarcely seems to be any increase in carbon dioxid output, but at the lower temperatures the quantity of the fat metabolism is markedly increased, as shown by the rise of carbon dioxid elimination. The individual sat quietly in a chair, but at a temperature of 4.4° could not prevent himself from shivering.

The whole effect of the chemical regulation in man has been attributed by Johansson[2] to the additional metabolism due to shivering. Voit did not believe that this could be the cause, nor that the increased respiratory activity could account for the rise in metabolism. Voit believed the increase to be a reflex stimulus of cold on the skin which raised the power of the muscle cells to metabolize. Voit's views have been confirmed in Rubner's laboratory[3] in the following series of experiments on a man:

Temperature.	CO_2 in Grams per Hour.
15°	32.3
20°	30.0
23°	27.9
25°	31.7
29°	32.4

[1] Voit: "Zeitschrift für Biologie," 1878, Bd. xiv, p. 80.

[2] Johansson: "Skan. Archiv für Physiologie," 1896, Bd. vii, p. 123.

[3] Rubner: "Energiegesetze," 1902, p. 203.

In this experiment there was no shivering at a temperature of 15° and yet the metabolism increased from what it was at 23°.

It has also been shown that cool baths and winds increase the metabolism, which must be effected through the chemical regulation. Lefèvre[1] states that a man, who has been inured to it, may sit naked for several hours in a cold wind without a reduction of body temperature.

Rubner[2] has measured the effect of baths and douches lasting three and a half to five minutes. When the water has a temperature of 16° he finds that the carbon dioxid elimination may be very largely increased, especially in the case of the douche. The effect of the douche was more marked if taken before breakfast when the intestinal tract is free from food. The results before breakfast were as follows:

INFLUENCE OF COLD BATHS ON METABOLISM IN MAN.

	Douche 16°. Increase in per Cent.	Bath 16°. Increase in per Cent.
Volume of respiration	54.5	22.9
Carbon dioxid excreted	149.5	64.8
Oxygen absorbed	110.1	46.8

A cold bath, especially a douche, will therefore stimulate to a greatly increased metabolism. The mechanical stimulus of the falling cold water apparently acts reflexly to increase the metabolism greatly, as it certainly does the magnitude of the respiration. The respiratory quotient indicates that the increased metabolism is at the expense of the glycogen supply. There is an after-effect which lasts about one and a half hours, indicating an increased metabolism during that time. This may be the expression of the body's attempt to maintain a normal temperature after being somewhat cooled (see also p. 318).

It is obvious that a cold bath will be likely to induce shiver-

[1] Lefèvre: "Comptes rendus," 1894, p. 604.

[2] Rubner: "Archiv für Hygiene," 1903, Bd. xlvi, p. 390.

ing unless by mechanical effort, such as swimming, the metabolism is increased so as to supply calorific energy in another way than through chemical regulation (see p. 193).

A bath of 35° has no effect on metabolism.

Rubner finds that a bath at 44° again increases the metabolism, the increase being, for the volume of respiration, 18.8 per cent., for carbon dioxid 32.1 per cent., and for oxygen 17.3 per cent. This is probably due to the overwarming of the cells. Baths at this temperature find favor among the Japanese.

The effect of wind is such that an imperceptible air current may have a very pronounced effect. Rubner[1] has shown that wind becomes perceptible when it attains a velocity of 0.4 to 0.5 meter a second, and that if a wind much below this *threshold* value, having a velocity of 0.18 meter per second, act upon the exposed area of the arm, there is an increased heat loss of between 19 and 75 per cent., depending on the temperature of the wind, above what would be lost were the air quiet.

The effect of wind of moderate humidity and different temperatures on the metabolism of a man clad in summer clothes, as compared with the metabolism during atmospheric calm, is shown in Wolpert's[2] experiment below:

INFLUENCE OF WIND ON METABOLISM IN MAN.

Temperature.	Calm.	Wind 1 Meter per Second.	Wind 8 Meters per Second.
	Grams CO_2 per Hour.	Grams CO_2 per Hour.	Grams CO_2 per Hour.
2°	29.8	....	....
10–15°	25.1	28.3	30.0
15–20°	24.1	....	30.1
20–25°	25.0	....	28.0
25–30°	25.3	22.2	24.4
30–35°	23.7	....	21.6
35–40°	21.2	22.2	22.1

[1] Rubner: "Archiv für Hygiene," 1904, Bd. l, p. 296.

[2] Wolpert: *Ibid.*, 1898, Bd. xxxiii, p. 206.

According to this, a breeze having a temperature of 15° to 20° and moving at the rate of about 15 miles per hour (8 meters per second) has a greater effect upon the metabolism of a man clad in summer clothing than a temperature of 2° would have during perfect atmospheric quiet. In all the experiments the smallest amount of carbon dioxid is eliminated between 30° and 40°.

The above experiments were performed on a thin man, and it will be noticed that there was no rise in his metabolism at a temperature of between 35° and 40°. Rubner explains this as due to the sufficiency of the evaporation of perspiration on the surface for the cooling of the organism.

A fat man, however, with a thick, ill-conducting layer of adipose tissue, is not so immune to the effect of high temperatures upon his metabolism. This is especially pronounced in a damp climate. Thus Rubner[1] obtains the following results from a fat man wearing clothes:

INFLUENCE OF TEMPERATURE AND HUMIDITY ON THE METABOLISM OF A FAT MAN.

Temperature.	Humidity 30 per Cent.		Humidity 60 per Cent.	
	CO_2 in grams per hour.	H_2O evaporated per hour.	CO_2 in grams per hour.	H_2O evaporated per hour.
20°	33.7	56	30.7	17
28–30°	36.9[1]	134	44.5[3]	170 + 31 g. sweat.
36–37°	42.6[2]	204 + 14 g. sweat.	46.7[4]	186 + 255 g. sweat.

[1] Body temperature rose 0.1°
[2] " " " 0.0°
[3] Body temperature rose 0.4°
[4] " " " 0.9°

The fact that in the experiment where there was 30 per cent. humidity the metabolism largely increased at 36° to 37° without concomitant rise in body temperature, leads Rubner to theorize that there must have been an overheating of the cells where the

[1] Rubner: "Energiegesetze," 1902, pp. 208, 232.

metabolism was progressing, even though this might not have been determinable by the clinical thermometer.

It appears that on a hot, humid day the metabolism of a fat individual may be fifty per cent. higher than on a day of moderate temperature and the same humidity. The whole of the body heat is lost through the evaporation of water which is here hindered by the humidity. There is a large and exhausting excretion of sweat which on account of the difficulty in evaporation is not effective in cooling the body. At a moderate temperature, where the greater part of the heat loss is by radiation and conduction, the excretion of water is not excessive.

There can be no doubt that climatic conditions modify racial characteristics. The emigrant from northern Europe, living upon a farm in the hot and often moist climate of an American summer, must restrict his layer of adipose tissue if he is to live comfortably. The same holds true in Italy. The difference between John Bull and Uncle Sam seems to be one of climatic adaptation. On the contrary, the Eskimo cultivates a thick, fat layer to protect himself from frost. It is also interesting to note that prostrations from the heat appear in New York with 66 per cent. humidity and a temperature of 31.5° (2.30 P.M., August 24, 1905). Rubner[1] says that a lightly clad thin man, at a temperature of 30° with humidity at 65 per cent., bore the effect so badly that he feared to raise the temperature to 35°. This individual had readily tolerated 35° in dry air.

The maximum mortality from "summer troubles" in children in New York coincides with the first great wave of heat accompanied by humidity which falls upon the city. Similar climatic conditions at later dates are not so fatal. It may be that the fatality of these intestinal affections is due to the inefficiency of the apparatus for the physical discharge of heat in the infant organism. It is also possible that infection may be more readily achieved under these conditions (p. 217).

Another factor in the heat regulation of man is clothes.

[1] Rubner: "Energiegesetze," 1902, p. 232.

Certain savage races living in cool climates do without clothes, as, for example, natives of Terra del Fuego, who substitute a covering of oil. In such races the process of "hardening" or the development of the physical regulation must be carried to a maximum. In civilized countries man endeavors to remove all the influence of chemical regulation by keeping his skin covered. Only about 20 per cent. of his surface is normally exposed to the air. The most important constituent of clothes is the air, which is a much worse conductor of heat than is the fiber. This is especially true of furs (p. 93). Thickness of the cloth will give a greater layer of air and will prevent heat loss from the body. A densely woven cloth prevents proper ventilation and does not absorb moisture. In hot weather a porous cloth next to the skin which can absorb moisture and permit its ready evaporation is of high importance. If a garment worn next to the skin become thoroughly wet the evaporation of sweat at a high temperature is largely prevented, to the great discomfort of the individual, while at a lower temperature heat loss through conduction is greatly facilitated, with a sensation of chill. Two experiments cited by Rubner[1] indicate the effect of clothes on metabolism. An individual was kept at a temperature of between 11° and 12° and wore different clothes at different times. His carbon dioxid and water excretion were as follows:

INFLUENCE OF CLOTHES ON METABOLISM IN MAN AT A TEMPERATURE OF 11° to 12°.

	CO_2 IN GRAMS PER HOUR.	H_2O IN GRAMS PER HOUR.	REMARKS.
Summer clothes	28.4	58	Cold, occasional shivering.
Summer clothes and winter overcoat	26.9	50	Chilly part of the time.
Summer clothes and fur coat	23.6	63	Comfortably warm.

[1] Rubner: "Energiegesetze," 1902, p. 225.

When the man was comfortable the chemical regulation of temperature was eliminated.

Rubner remarks that while the radiant energy of the sun is large in quantity, he has been unable to find any influence upon a man under ordinary circumstances, but believes that it may take the place of heat produced through chemical regulation on cold days. Thus a person living in the high altitude of Davos, Switzerland, feels much more comfortable in the sun on a cold day than he does in the shade. However, Zuntz while living on the summit of Monte Rosa found that sunlight did not reduce metabolism (p. 260).

In what follows it will be shown that the ingestion of food may add to the heat production of the organism and diminish the necessity of heat production through chemical regulation in cold weather. Also, it may very uncomfortably increase the production of heat and perspiration in warm weather, especially if protein be largely taken (p. 217).

From this chapter the influence of climate is seen to be noteworthy. It explains why a temperature of —40° may be comfortably borne in winter, in the Adirondacks, for example, if the air be dry and still; why a much warmer atmosphere which is damp and windy may "cut to the bone" with cold; why a hot, dry climate may be entirely comfortable, when air at the same temperature laden with moisture may strike down many fatally and oppress every one; and how the effect of heat may be modified by the breezes and baths at the seashore. It does not explain the effect of the dry sirocco wind which blows from the Desert of Sahara, the universal depressant action of which has been attributed to unknown cosmic influences.

CHAPTER IV.

THE INFLUENCE OF PROTEIN FOOD.

PART ONE.

It has been thought that protein is a food which is in itself sufficient for all the requirements of the body. Pflüger[1] was able to keep a very thin dog in good condition and doing active exercise during a period of seven months, the sole diet being meat cut as free from fat as possible. Pflüger says that the fat and glycogen content of the meat ingested could not have yielded sufficient energy to provide for the action of the heart alone. It must be remembered, however, that meat is not pure protein but is mixed with salts and water. The simplest diet capable of maintaining the body in condition is therefore a mixture of materials, or foodstuffs. Such a mixture of foodstuffs is called a food. A foodstuff is a material capable of being added to the body's substance, or one which when absorbed into the blood-stream will prevent or reduce the wasting of a necessary constituent of the organism.

The foodstuffs are:

Proteins (including albuminoids).
Carbohydrates.
Fats.
Salts.
Water.

A food is a palatable mixture of foodstuffs which is capable of maintaining the body in an equilibrium of substance, or capable of bringing it to a desired condition of substance. The ideal food is a palatable mixture of foodstuffs arranged together in such proportion as to burden the organism with a minimum of labor. These definitions are Voit's.[2]

[1] Pflüger: "Pflüger's Archiv," 1891, Bd. l, p. 98.

[2] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, pp. 330, 344.

If, instead of natural foods, purified materials such as casein, egg albumin, vitellin, potato starch, wheat starch, and oleomargarine together with the proper salts be mixed and given to mice, it has been shown by Röhmann[1] that the offspring are difficult to rear on the same food, and no living young can be obtained from them. Artificial foods will therefore not replace the natural products. Commercial preparations of meat are not so digestible as meat itself.[2]

When protein alone is ingested by a normal adult it is very readily oxidized, and is only with the greatest difficulty deposited so as to form new tissue in the organism.

In the early experiments of Bischoff and Voit, the fact is recorded that a dog weighing 35 kilograms may excrete 12 grams of urea in twenty-four hours, and the same dog after receiving 2500 grams of meat may excrete 184 grams, fifteen times as much.

Voit[3] has shown that if that quantity of meat be administered which corresponds to what is oxidized in starvation, nitrogen equilibrium will not be established, but some of the body's flesh will also be metabolized. This latter quantity grows steadily less if the amount of meat ingested be gradually increased until finally the point of *nitrogen equilibrium* is reached, at which the amount of meat ingested is equal to that destroyed in the body. To illustrate this Voit gives the following table, the results of work done on a dog:

Grams Meat Administered.	Grams Flesh Destroyed.	Change in the Body.
0	233	—233
0	190	—190
300	379	—79
600	665	—65
900	941	—41
1200	1180	+20
1500	1446	+54

Nitrogen equilibrium was not reached until 1200 grams of meat were given, or about five times the amount of the fasting protein metabolism.

[1] Röhmann: "Klinischer therapeutische Wochenschrift," 1902, No. 40.

[2] Poda and Prausnitz: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 377.

[3] Voit: *Loc. cit.*, 1881, p. 106.

The above experiments were made in 1858. It is no longer customary to calculate the protein metabolism in terms of flesh destroyed, but in terms of nitrogen. The old-fashioned term flesh meant meat with a nitrogen content of 3.4 per cent. It served to illuminate the significance of metabolism at a time when few were instructed in this field of work.

E. Voit and Korkunoff[1] have published a research of similar character. They fed a dog with meat which had been treated with lukewarm water to remove the extractives, and which was then squeezed in a press. This process removes most of the nitrogen-containing substances other than protein. A dog will readily eat this washed meat or "protein." The idea was to determine the minimum quantity of protein which it was possible to ingest and still maintain nitrogen equilibrium. The different quantities of meat tabulated below were given continuously for two or three days at a time. Only the results of the last day of each of these periods are quoted:

Food.	N in Food.	N in Excreta.	Difference.
Starvation	0	3.996	—3.996
100 g. meat	4.10	5.558	—1.458
140 g. "	5.74	6.495	—0.755
165 g. "	6.77	7.217	—0.447
185 g. "	7.59	7.804	—0.214
200 g. "	8.20	8.726	—0.526
230 g. "	10.24	10.579	—0.339
360 g. "	11.99	12.052	—0.062
410 g. "	15.58	14.314	+1.266
360 g. "	13.68	13.622	+0.058
Starvation, third day	....	4.026	—4.026

The figures show that nitrogen equilibrium was reached only after supplying three and a half times the amount of protein metabolized in starvation. The authors calculate that at this time of nitrogen equilibrium the dog was still losing 28 grams of body fat, and that not much more than fifty per cent. of the total energy liberated in the organism was furnished by the protein metabolism of the time. *One may thus have nitrogen equilibrium without having carbon equilibrium.*

[1] E. Voit and Korkunoff: "Zeitschrift für Biologie," 1895, Bd. xxxii, p. 58.

Systems of diet for fat people are based on this knowledge. A loss of protein is highly undesirable, while a gradual loss of adipose tissue may be a great relief to the obese.

Bornstein[1] finds that during a period of thirteen days he can add 8.3 grams of protein to his body and oxidize 90 grams of body fat daily, when ingesting a mixed diet containing 1600 calories with 118 grams of protein. Such a diet contains a fuel value less than the requirement of his organism (p. 182).

If the quantity of meat ingested be steadily increased after nitrogenous equilibrium has been reached, the protein metabolism will gradually increase, nitrogenous equilibrium will be established at higher and higher levels, and there will be a corresponding diminution in the amount of fat burned. This was shown in the following experiment of Voit,[2] who gave different quantities of meat to a large dog weighing 30 kilograms.

INFLUENCE OF INGESTING INCREASING QUANTITIES OF MEAT.

Weights are in Grams.

Meat Ingested.	Flesh Destroyed.	Gain or Loss of Body Flesh.	Gain or Loss of Body Fat.	Respiratory Quotient.
0	165	—165	—95	.72
500	599	—99	—47	.76
1000	1079	—79	—19	.74
1500	1500	0	+4	.81
1800	1757	+43	+1	—
2000	2044	—44	+58	.84
2500	2512	—12	+57	—

Nitrogen equilibrium existed after the ingestion of 1500 grams of meat and there was also no loss of body fat (carbon equilibrium). When 2000 grams and even 2500 grams of meat were supplied it was all destroyed, as was indicated by the amount of nitrogen in the urine, but a certain quantity of carbon belonging to the ingested protein was not eliminated in the respiration but was retained in the body. This carbon Pettenkofer and Voit believed to have been laid up in the body in the form of fat.

[1] Bornstein: "Berliner klinische Wochenschrift," 1904, No. 46.

[2] Voit: "Stoffwechsel," 1881, p. 117.

The respiratory quotient in the foregoing series gradually rises, as would be expected from the increasing prominence of the protein in the metabolism (p. 28). Meat alone will therefore support a dog. Rubner[1] says that a man cannot live on meat alone, not because the intestinal canal cannot digest it, but because of the physical limitations of the apparatus of mastication.

A subject of interest in considering the value of protein in metabolism is that of the value of gelatin. Gelatin is an artificial derivative of collagen, an albuminoid largely found in the skeletal structure of animals. Gelatin contains very nearly the same quantity of nitrogen as protein; it breaks up on chemical treatment into the same amino-acids, except that it does not yield tyrosin, cystin, and tryptophan. In the diabetic, gelatin yields the same amount of sugar as does protein.[2] To what extent gelatin may take the place of protein in the body's metabolism has long been the subject of inquiry.

It was shown first by Bischoff and Voit[3] that no matter how much gelatin was ingested it was always completely burned and some of the body's protein in addition. Therefore gelatin never builds up new tissue, although it may somewhat diminish tissue waste. Gelatin may be formed from protein in the body, but it cannot be reconverted into protein nor act like protein in metabolism. Kirchmann,[4] working in the laboratory of Erwin Voit, has shown to what extent gelatin spares protein in metabolism. If one takes the amount of protein metabolism in starvation as one, then the ingestion of about the same quantity of gelatin reduces the body's protein waste 23 per cent., and if eight times this amount of gelatin be given, the tissue waste may be reduced 35 per cent. In other words, the ingestion of 7.5

[1] Rubner: von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 42.

[2] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, vol. i, p. 395.

[3] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, p. 396.

[4] Kirchmann: "Zeitschrift für Biologie," 1900, Bd. xl, p. 54.

per cent. of the total heat requirement of the organism in the form of gelatin spares 23 per cent. of the body's protein, while the ingestion of 60 per cent. of the requirement will only cause a decrease of 35 per cent. in protein waste. Krummacher[1] showed that the ingestion of the full heat requirement of the animal in the form of gelatin reduced the fasting protein metabolism by only 37.5 per cent. It is evident that no matter how much gelatin be given, tissue protein continues to be destroyed, and it is also evident that a small quantity of gelatin has almost as great an effect as a large quantity.

An extremely interesting experiment of Kauffmann[2] shows that when the lacking tyrosin, cystin, and tryptophan are mixed with gelatin in the proportions in which they occur in true protein, and are given to a dog or to a man, nitrogen equilibrium may be established.

It is evident from this experiment that the value of the various proteins in nutrition may depend upon their constituent amino-acids, and for this reason the table on p. 113 of the composition of vegetable and animal proteins as furnished by the fundamentally valuable work of Osborne and of Abderhalden has been compiled.

Concerning the crystalline vegetable proteins which he has investigated Osborne[3] writes: "It is possible to establish a constancy of properties and ultimate composition between successive fractional precipitations which give no reasons for believing the substance to be a mixture of two or more individuals. On chemical grounds there is no more reason for dividing the proteins into two groups of animal and vegetable proteins than there is in making a similar distinction between the carbohydrates. Of twenty-three seed proteins which have been hydrolized all have yielded leucin, prolin, phenylalanin, aspartic acid, glutamic acid, tyrosin, histidin, arginin and ammonia.

[1] Krummacher: *Ibid.*, 1901, Bd. xlii, p. 242.
[2] Kauffmann: "Pflüger's Archiv," 1905, Bd. cix, p. 440.
[3] Osborne: "Science," 1908, vol. xxviii, p. 417.

Glycocoll, lysin, and tryptophan are the only amino-acids which have been proved lacking in any one of these proteins. Nothing is known of the undetermined residue which forms from twenty-five to thirty-five per cent. of the protein. We may expect to find still undiscovered substances among the protein decomposition products."

PERCENTAGE COMPOSITION OF PROTEINS.

	Serum Albumin.*	Serum Globulin.*	Syntonin* from Muscle.	Cow's Casein.*	Gelatin.†	Gliadin from Wheat.‡	Glutenin from Wheat.‡
Ammonia	..	..	..	..	..	5.11	4.01
Glycocoll	0	3.5	0.5	0	16.5	0	0.89
d-Alanin	2.7	2.2	4.0	0.9	0.8	2.00	4.65
d-Valin	..	+	0.9	1.0	1.0	0.21	0.24
l-Leucin	20.0	18.7	7.8	10.5	2.1	5.61	5.95
l-Serin	0.6	..	..	0.2	0.4	0.13	0.74
Cystin	2.3	0.7	..	0.06	..	0.45	0.02
l-Aspartic acid	3.1	2.5	0.5	1.2	0.6	0.58	0.91
d-Glutamic acid	7.7	8.5	13.6	11.0	0.9	37.33	23.42
Lysin	..	..	..	5.8	2.7	0	1.92
d-Arginin	..	..	..	4.8	7.6	3.16	4.72
l-Phenylalanin	3.1	3.8	2.5	3.2	0.4	2.35	1.97
Tyrosin	2.1	2.5	2.2	4.5	0	1.20	4.25
l-Prolin	1.0	2.8	3.3	3.1	5.2	7.06	4.23
l-Oxyprolin	..	..	..	0.2	3.0	..	..
l-Tryptophan	+	+	..	1.5	0	+	+
l-Histidin	..	..	..	2.6	0.4	0.61	1.76
Total	42.6	45.2	35.3	50.6	41.6	65.80	59.68

\+ signifies present.
* Abderhalden.
† Fischer, Levene and Aders.
‡ T. B. Osborne.

In recent years the idea has been gaining ground that protein bodies must be broken up into amino-acids before absorption in the intestine (p. 186). If this be true then ingestion of the cleavage products of protein should maintain nitrogen equilibrium in the same way as the ingestion of meat. The first experiments in this direction were done by Loewi,[1] who gave a dog pancreas which had been self-digested until all the protein

[1] Loewi: "Archiv für ex. Path. und Pharm.," 1902, Bd. xlviii, p. 303.

had been converted into amino-acids, as was indicated by the almost complete disappearance of the biuret reaction. Fat and carbohydrates were given with the digest, and nitrogen equilibrium was obtained and even nitrogen retention accomplished. Thus, in one experiment covering a period of eleven days, proteolytic digestive products containing an average of 6.08 grams of nitrogen were given daily, of which only 5.19 grams were eliminated in the urine, while the balance, or 0.89 gram of nitrogen, was retained in the body of the animal. This amounted to 9.79 grams of nitrogen in eleven days. Accompanying this nitrogen retention was one of 0.649 gram of phosphoric acid (P_2O_5), an amount larger than was necessary for the upbuilding of new tissue from the nitrogen compounds retained. Loewi concluded that he had demonstrated the synthesis of new protein within the organism.

Lesser[1] gave a pancreatic digest of fibrin to a dog and was unable to obtain nitrogen equilibrium.

Henderson and Dean[2] confirmed Loewi by finding that they could obtain nitrogen equilibrium by feeding a dog with the cleavage products of meat produced by treatment with sulphuric acid.

Stiles and Lusk,[3] on the contrary, gave a fasting diabetic dog a pancreatic digest of meat which had undergone fourteen months of proteolytic cleavage, and observed that the nitrogen of it was completely eliminated in the urine without protecting the body from loss of protein, which protection would have occurred had meat itself been administered.

To reconcile these differences it seemed necessary to consider the differences in methods of preparing the end products of the protein to be ingested. Indeed, Abderhalden and Rona[4]

[1] Lesser: "Zeitschrift für Biologie," 1904, Bd. xlv, p. 506.

[2] Henderson and Dean: "American Journal of Physiology," 1903, vol. ix, p. 386.

[3] Stiles and Lusk: "American Journal of Physiology," 1903, vol. ix, p. 380.

[4] Abderhalden and Rona: "Zeitschrift für physiologische Chemie," 1904, Bd. xlii, p. 528.

find that mice live on casein split with pancreatin as long as they do on casein alone; whereas they die much earlier if the casein has been submitted to peptic and then pancreatic digestion, or if it has been broken up by acid hydrolysis. Henriques and Hansen[1] also find that casein broken up by acid will not maintain nitrogen equilibrium in rats, but that if the pancreas of the ox and a small piece of the intestine of the dog (to furnish erepsin) be digested for two months at 40°, and the resulting material given to rats, nitrogen equilibrium will be maintained. The authors further find that the monoamino-acid fraction (the filtrate after precipitation with phosphowolframic acid), and also the alcoholic extract of the last-named digest, maintain rats in nitrogen equilibrium. The residue left after alcoholic extraction will not do so.

Abderhalden and Rona[2] have accomplished a most interesting experiment upon a dog. The animal was given daily a constant quantity of non-nitrogenous foods which were: fat, 25 grams; starch, 50 grams; cane sugar, 10 grams; dextrose, 5 grams. The dog was brought into nitrogen equilibrium by giving meat containing 2 grams of nitrogen. Then for this were substituted the amino cleavage products of casein, produced by pancreatic digestion and also containing 2 grams of nitrogen. During sixteen days on this diet there was an average daily gain of 0.12 gram of nitrogen by the dog. Then casein hydrolized by acid and containing 2 grams of nitrogen was administered for ten days, during which time the dog lost 0.48 gram of nitrogen daily. Amino-products prepared after this fashion will therefore not preserve nitrogen equilibrium. Lastly, the diet was continued without any nitrogenous food. The daily waste of body nitrogen was then 0.53 gram. The loss was the same as when the casein hydrolized by acid was ingested, indicating that this particular array of cleavage products had no protecting power over the body protein.

[1] Henriques and Hansen: *Ibid.*, 1905, Bd. xliii, p. 417.

[2] Abderhalden and Rona: *Ibid.*, 1905, Bd. xliv, p. 198.

The absence of virtue in the casein hydrolized by acids is attributed by Abderhalden and Rona[1] to the complete destruction of all polypeptids (p. 59), which they consider to be the constructive nuclei (Bausteine) of protein. When the latter are present a partial reconstruction of amino-acids into the proteins of blood serum is possible.

Henriques[2] has hydrolized protein by digesting it with trypsin and erepsin and then treating with 20 per cent. sulphuric acid on the water bath. The resulting material consists entirely of amino-acids with no admixture of polypeptids, and if it still gives a pronounced tryptophan reaction it will support the organism in nitrogen equilibrium. *In the absence of the single amino-acid tryptophan, nitrogen equilibrium cannot be attained.*

It seems therefore proved that amino-bodies resulting from certain proteolytic cleavages may be the equivalent in metabolism of ingested protein itself.

In practical dietetics these substances can have no value, as they tend to produce diarrhea, as do also albumoses and peptones when given in any considerable quantity.[3] As illustrating this, Cronheim[4] finds that though "Somatose" is more digestible than meat, still over 30 grams is undesirable in the daily diet of a man.

It is certain that if there be a new construction of protein in the body from the amino-acids formed in digestion such new proteins are characteristic of the organism, and do not possess the properties of the proteins originally ingested. To illustrate this Abderhalden and Samuely[5] gave to a horse 1500 grams of gliadin, a vegetable protein which contains 36.5 per cent. of glutamic acid. They wondered if the ingestion of

[1] Abderhalden and Rona: "Zeitschrift für physiol. Chemie," 1906, Bd. xlvii, p. 397.

[2] Henriques: "Zeitschrift für physiologische Chemie," 1907, Bd. liv, p. 406.

[3] Voit: "Münchener med. Wochenschrift," 1899, Nos. 6 and 7.

[4] Cronheim: "Pflüger's Archiv," 1904, Bd. cvi, p. 17.

[5] Abderhalden and Samuely: "Zeitschrift für physiologische Chemie," 1905, Bd. xlvi, p. 193.

such a protein would in any way modify the composition of the proteins of the blood serum, of serum globulin which under ordinary circumstances contains 8.5 per cent., and of serum albumin which contains 7.7 per cent. of glutamic acid. Their results were as follows:

INFLUENCE OF GLIADIN INGESTION ON THE PER CENT. OF GLUTAMIC ACID IN THE SERUM PROTEINS OF THE HORSE.

Experiment.	Normal Day.	After Fasting 7 or 8 Days.	After Ingesting 1500 G. Gliadin. Day 1.	Day 2.
I	8.85	8.20	7.88	8.25
II	9.52	8.52	8.00	...

It is evident that gliadin which contains so large a proportion of glutamic acid is without influence on the composition of the blood serum. The larger part of the glutamic acid is probably deaminized in the intestinal wall before reaching the blood. Abderhalden conceives that such proportions of the amino-acids within the gliadin complex as are available for the formation of new serum albumin and serum globulin are used for the generation of these proteins.

It has already been stated (p. 58) that if the serum of a dog be injected into the blood-vessels of another dog the nitrogen of it will be eliminated in the urine. This is also true of proteins foreign to the organism, and these likewise act in a toxic manner to destroy body protein. Thus Mendel and Rockwood[1] have shown that if edestin, a pure crystalline protein prepared from hemp seed, be injected intravenously into a fasting dog, there is for two days a metabolism of protein which is much greater than that of former days plus that of the edestin administered. The same truth holds when casein is injected. Similar injection of horses' serum into dogs appears to have no toxic action (Rona and Michaelis[2]). This work is of interest in connection with the subject of *anaphylaxis*, called also the

[1] Mendel and Rockwood: "American Journal of Physiology," 1904, vol. xii, p. 350.

[2] Rona and Michaelis: "Pflüger's Archiv," 1908, cxxi, p. 163; and 1908, cxxiii, p. 406.

Theobald Smith phenomenon, which has been especially investigated by Rosenau and Anderson. Injections of a protein foreign to the organism render the body sensitive to a second injection of the same protein. Large or small amounts of foreign protein may be injected in the first instance without intoxication, but if the animal be once "sensitized" a small amount of the same protein will terminate the animal's existence. It has recently been stated by Wells[1] that the injection of so minimal an amount as one millionth of a gram of pure crystalline egg albumin will "sensitize" a guinea pig so that a subsequent injection into the blood of a tenth of a milligram of the same substance is lethal, although such a dose given in the first instance would not have injured the animal. It is evident, therefore, that the alimentary canal cannot allow the passage of proteins without changing them. This also explains the complete immunity of the organism to snake venom which has been swallowed.

The effect of copious drinking of water upon protein metabolism has been made the subject of various studies. A small increase in nitrogen elimination has usually been noted. This was first established by Voit, who explained it as due to an increased circulation which influenced the flow of the intracellular fluids. Heilner[2] has recently shown that giving 2000 c.c. of water to a fasting dog on two successive days raises his urinary nitrogen from 3.15 grams to 4.09 and 3.58 grams on the two days of water ingestion, and then the nitrogen excretion falls to 2.22 and 2.62 on the following days. In this experiment the carbon dioxid excretion was very slightly increased and the temperature of the dog was not affected. The quantity of urine rose from 90 c.c to 2050 c.c.

Straub[3] found that an extra ingestion of 2000 c. c. of water

[1] Wells: Proceedings of the Society for Experimental Biology and Medicine, 1908, vi, p. 1.

[2] Heilner: "Zeitschrift für Biologie," 1906, Bd. xlvii, p. 541.

[3] Straub: *Ibid.*, 1899, Bd. xxxvii, p. 527.

in a man who was in nitrogen equilibrium on a diet containing 20.56 grams of nitrogen had no effect on protein metabolism; whereas Hawk,[1] who gave less protein nitrogen but more water, found that the ingestion of 4500 c.c. of water caused the urinary nitrogen to rise from 11.03 to 12.48 on the first day, and 11.82 on the second day, with a fall to 10.91 grams on the succeeding day when no water was given. Hawk interprets the action of copious water-drinking as twofold,—*first*, to cause a removal of any accumulation of nitrogenous decomposition products from the organism, as was indicated by the greater increase of 12.8 per cent. in the nitrogen elimination of the first day; and, *second*, to cause a true increase in protein metabolism, as was indicated by the smaller increase of 6.8 per cent. on the second day of water ingestion.

Abderhalden and Bloch[2] have given a fixed diet to a person suffering from alkaptonuria (see p. 136) and on one of the days of the experiment have caused him to ingest 5 liters of water. The results of their analyses gave the following figures:

	N Balance.	N in Urine.	Homogentisic Acid.
Normal Food	+ 1.36	18.2	10.52
" " + 5 L. Water	— **2.19**	**21.75**	**10.18**
" "	+ 1.47	18.09	10.27

Abderhalden believes that the constancy of the output of homogentisic acid indicates a constancy of protein metabolism throughout, whereas the rise in total nitrogen elimination in the urine represents a washing out of the nitrogenous end-products as a result of the large ingestion of water.

One of the striking characteristics of starvation metabolism was shown to be its extreme regularity from hour to hour and from day to day. What, then, is the hour-to-hour metabolism after meat ingestion?

[1] Hawk: "University of Pennsylvania Medical Bulletin," March, 1905.

[2] Abderhalden and Bloch: "Zeitschrift für physiologische Chem.," 1907, Bd. 53, p. 464.

The classical experiments of Voit[1] and of Feder[2] have been more fully worked over by Gruber. Gruber[3] fed a dog with 500, 1000, and 1500 grams of meat on different days. He collected the urine every two hours after the meal and determined the nitrogen output. The curves of nitrogen elimination under these circumstances are as follows:

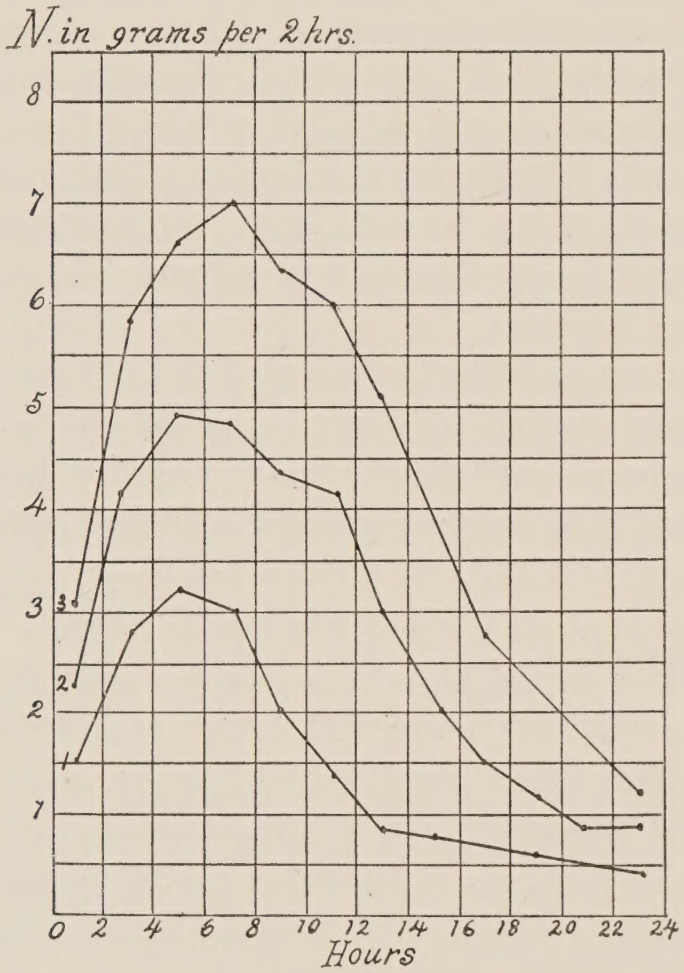


Fig. 5.—1, after 500 g. meat + 50 g. fat + 350 c.c water; 2, after 1000 g. meat + 200 c.c. water: 3, after 1500 g. meat + 500 c.c. water. On each of these days the animal was in nitrogen equilibrium.

It is evident that there is an early elimination of protein nitrogen which here reaches a maximum between five and seven

[1] Voit: "Physiologische Untersuchungen," Augsburg, 1857, p. 42.
[2] Feder: "Zeitschrift für Biologie," 1881, Bd. xvii, p. 541.
[3] Gruber: *Ibid.*, 1902, Bd. xlii, p. 421.

hours after feeding, and that the hour of the maximum excretion is delayed by increasing the quantity of meat ingested.

It is apparent, therefore, that the protein metabolism as illustrated by the curve of nitrogen elimination is quite different from the even metabolism of starvation.

Haas[1] in experiments on man finds that the curve of nitrogen elimination after a breakfast consisting of milk, bread, butter, and cheese always shows two maxima, the first in the second hour and the second in the fifth. The first rise in the curve is due to the removal of nitrogenous end-products already in the system and is caused by the early absorption of liquids taken with the food. The second rise corresponds to the absorption of food-protein. Haas believes this to be the true explanation, because if diuresis be first induced by drinking tea, with a consequent washing out of urea from the body, then partaking of breakfast no longer causes so high a primary rise of nitrogen elimination, nor is the total elimination so great as in the experiments without preliminary diuresis. The experiment shows that for short periods the nitrogen excretion is not a true index of urea production. Severe muscular work has no influence upon the character of the curve described except when the quantity of urine produced is diminished, in which case the urea elimination is also reduced.

If protein is given to a fasting dog the rapidity of its destruction is greater the longer the animal has been fasting.[2]

If protein or amino-acids such as glycocoll[3] and aspartic acid are administered the resulting nitrogen increase in the urine is entirely due to urea.[4]

If in man various proteins be added to an already sufficient mixed diet (superposition experiments), the rate of destruction

[1] Haas: "Biochemische Zeitschrift," 1908, Bd. xii, p. 203.

[2] Falta and Gigon: "Biochemische Zeitschrift," 1908, vol. xiii, p. 269.

[3] Brugsch and Hirsch: "Zeitschrift für experimentelle Pathologie und Therapie," 1906, Bd. iii, p. 638.

[4] Levene and Kober: "American Journal of Physiology," 1909, vol. xxiii, p. 324.

of the added protein as indicated by the extra N eliminated in the urine varies with the character of the protein. Such experiments were first devised by Falta,[1] who established the following classification of proteins in the order of the rapidity of their destruction: *a.* gelatin, casein, serum albumin, fibrin; *b.* blood globulin; *c.* hemoglobin; *d.* egg albumin. Hämäläinen and Helme[2] continued these experiments and they also investigated the elimination of sulphur and phosphorus. They gave a man weighing 66 kilograms a diet containing 3650 calories and 5 grams of nitrogen. On this diet they superimposed on different days the following amounts of proteins:

800 g. white of egg = 14.40 g. N + 1.56 g. S
57 g. proton = 6.94 g. N + 0.419 g. S
320 g. veal = 13.44 g. N + 0.832 g. S

and noticed the time of the elimination of nitrogen, sulphur, and phosphorus through the kidney. It was six days before all the nitrogen of the ingested white of egg was eliminated, whereas that in veal and proton required only two or three days. This is evident from the following table:

DAILY PERCENTAGE ELIMINATION OF THE NITROGEN, SULPHUR, AND PHOSPHORUS OF INGESTED PROTEIN SUPERIMPOSED ON AN ADEQUATE DIET.

Day.	Egg-white.		Proton.		Veal.		
	N.	S.	N.	S.	N.	S.	P.
1	21	41.4	64	90	56	74.2	60
2	21	32.2	10	10	26	17.8	24
3	22	14.4	13	..	18	8.0	16
4	11	4.3	13	..	..	..	..
5	14	5.5	..	..	..	..	..
6	11	2.4	..	..	..	..	..

The rapidity of the sulphur elimination is everywhere noticeable. The "nitrogen lag" in the case of white of egg is

[1] Falta: "Deutsches Archiv für klinische Medizin," Bd. xxxvi, 1906, p. 517.

[2] Hämäläinen and Helme: "Skan. Archiv für Physiologie," 1907, Bd. xix, p. 182.

pronounced and may be due to the retention of peptids which are only slowly metabolized or it may be due to the retention of amino-acids themselves.

That glycocoll as such is normally present within the organism has already been mentioned in connection with the fact that when benzoic acid is ingested there is at first a considerable output of hippuric acid, and this is followed by a constant output of the substance in proportion to the protein metabolized. Furthermore Murlin[1] has shown that if glycocoll be ingested with carbohydrates, then instead of being converted into urea it is quite largely retained, so that nitrogen equilibrium is almost obtained on the first day of ingestion. On continuing the same diet, however, the capacity to retain the glycocoll diminishes, as is witnessed by the increasing elimination of nitrogen in the urine.

RETENTION OF GLYCOCOLL INGESTED WITH CARBOHYDRATES.

Day.		Cal. per Kg.	N in Urine.	N Balance.
1	5th day fasting.	...	1.288	—1.288
2	7 g. glycocoll — 1.332 N	142	1.457	—0.125
3	" "	142	1.612	—0.280
4	" "	142	2.006	—0.674
5		140	0.987	—0.987
6		140	0.713	—0.713

This experiment should be interpreted in the light of the fact that the carbohydrates ingested would of themselves reduce the fasting protein metabolism to one-third its original amount (*i. e.*, from 1.28 to 0.43 grams N; see p. 173). Since after removing glycocoll from the ingesta and continuing the liberal administration of carbohydrate the urinary nitrogen did not fall to one-third the fasting amount, Murlin concluded that this was due to a gradual elimination of the glycocoll nitrogen previously ingested.

[1] Murlin: "American Journal of Physiology," 1907, vol. xx, p. 250.

This experiment indicates why in the presence of carbohydrates protein nitrogen may be only slowly eliminated, and gives an elementary example of "nitrogen lag."

Lüthje[1] has noted a similar nitrogen retention after giving glycocoll and asparagin and has speculated on the formation of an "amino-sugar."

Dr. C. G. L. Wolf has kindly placed some unpublished work at the writer's disposal. Wolf gave a man a constant and sufficient diet containing 7 grams of nitrogen, of which 1.2 grams were given at breakfast and the rest at an evening meal. Upon the "normal" breakfast he "superimposed" different materials. The gross results of the experiments during twenty-four-hour periods were as follows:

Food Superimposed.				Balance to Body.	
Kind.	Grams.	Content of:		N.	S.
		N.	S.		
None (normal period).....				—2.0	—0.15
Veal cutlets.....	500	17.1	1.02	+ 8.7	+0.23
Urea.....	25	11.66	..	+*1.8	
Alanin.....	50	7.86	..	+*4.0	
Cystin.....	10	1.14	2.65	—0.5	+0.73

* Feces not analyzed.

The more detailed procedure included the analysis of the urine every hour for sixteen hours after ingestion of the breakfast, and some of the results are presented in the curve furnished by Dr. Wolf and shown in Fig. 6. The curve of total nitrogen elimination is here given and in every case this total nitrogen elimination consisted almost entirely of urea nitrogen.

After ingestion of the very soluble urea it is noticed that there is a rapid rise in the nitrogen elimination in the urine. The same is true after the ingestion of alanin, the nitrogen of which is rapidly converted into urea. The nitrogen of the veal cutlets,

[1] Lüthje: "Congress für innere Medizin," 1906, p. 44.

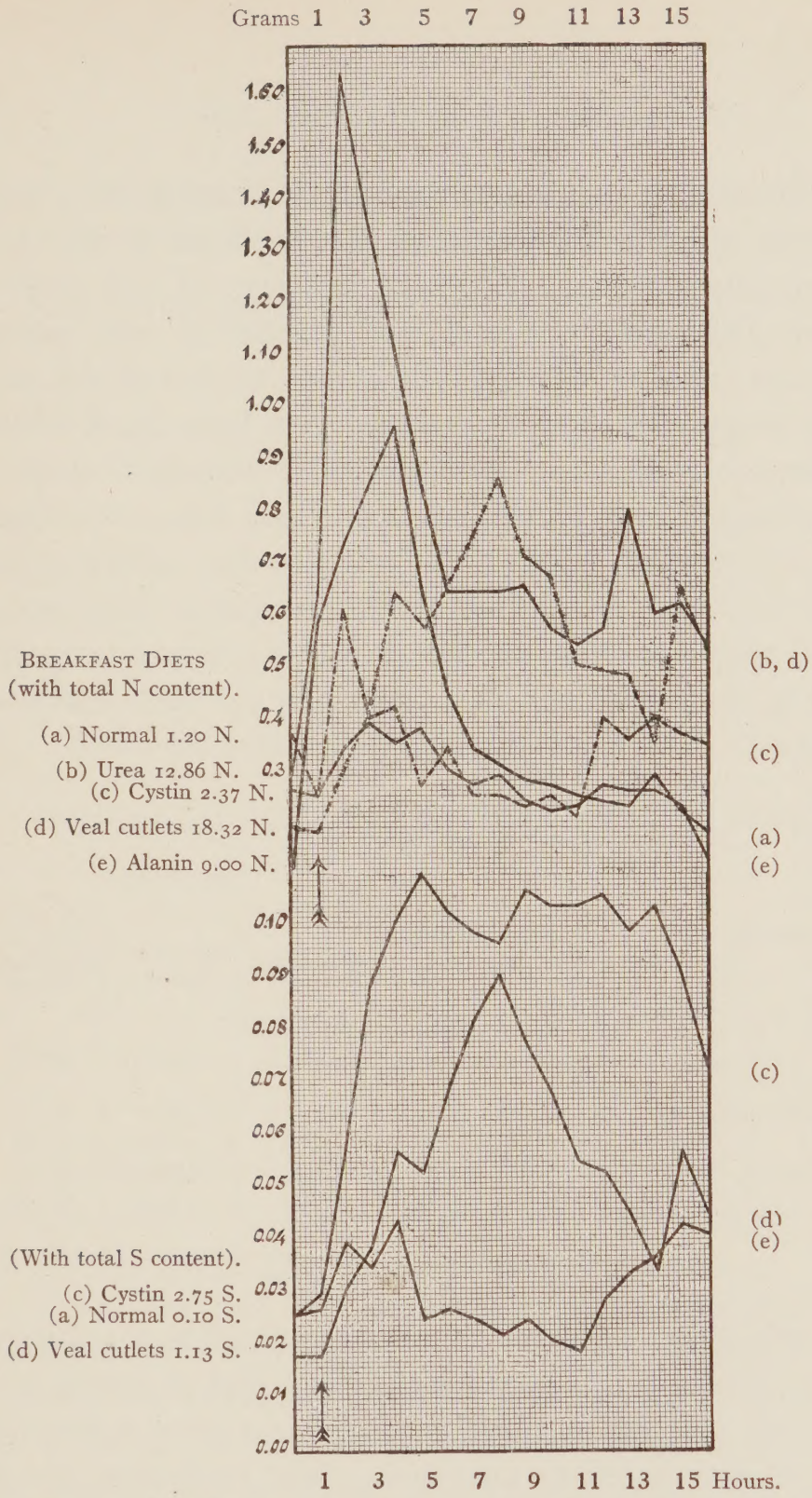


Fig. 6.—The different curves begin at the level of the excretion of urinary N or S determined during an early hour previous to breakfast. The *arrow* represents the time an hour after food ingestion, and shows no increased excretion, except in the cases of the very soluble urea and alanin. The *secondary rises* in the curves in the tenth to twelfth hours are due to the ingestion of supper.

Upper Part.—Represents the hourly excretion of total N after ingesting (a) "normal" breakfast containing 1.20 g. N; (b) same breakfast plus urea with 11.66 g. N; (c) same breakfast plus cystin with 1.14 g. N; (d) same breakfast plus veal cutlets with 17.1 g. N; (e) same breakfast plus alanin with 7.86 g. N.

Lower Part.—Represents excretion of S during the same intervals: (a) "normal" breakfast containing 0.1 g. S; (c) same breakfast plus cystin with 2.65 g. S; (d) same breakfast plus veal cutlets with 1.02 g. S.

however, requires a much longer time for its elimination. The sulphur from cystin is for the most part oxidized to sulphate and is gradually excreted. After the ingestion of veal cutlets the sulphur and nitrogen curves run parallel to each other.

If we turn from the nitrogen elimination to that of the carbon in the respiration, it will be found that here the elimination is comparatively even. Frank and Trommsdorf[1] gave a dog 1191 grams of meat which had been freed from extractives by means of lukewarm water. The nitrogen and carbon of the urine and feces and the carbon of the respiration were determined, and from these data the protein and fat metabolism were calculated in the usual manner. From this the heat produced was estimated. The essential results were thus tabulated:

VARIATION IN METABOLISM AFTER MEAT INGESTION.

Period.	No. of Hours.	Per Hour.		
		N in Urine.	C in Respiration.	Calories from Metabolism.
Starvation.....	24	0.1944	2.968	36.72
Meat Ingested:				
First period after meat	4 h. 9 m.	0.917	3.862	43.94
Second " " "	3 h. 14 m.	1.373	3.886	41.53
Third " " "	5 h. 44 m.	1.592	3.872	41.00
Fourth " " "	10 h. 53 m. (night)	1.064	3.493	38.46

It is evident that while the curve of the nitrogen elimination shows a maximum rise to nearly eight times that of fasting and varies greatly, the carbon curve is much more even and is not much above that found in starvation. The maximum rise in heat production occurs in the first four hours after the ingestion of meat and amounts to twenty per cent. The heat production falls during the night hours.

Rubner[2] has obtained similar results after giving 460 grams

[1] Frank and Trommsdorf: "Zeitschrift für Biologie," 1902, Bd. xliii, p. 266.

[2] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 365.

of washed meat to a dog weighing 24 kilograms. His calculations show the following metabolism during six-hour periods:

VARIATION IN METABOLISM AFTER MEAT INGESTION.

First Day of Ingestion.

Time of Day.	N in Urine.	Cal. from Protein.	Cal. from Fat.	Calories Total.
Day, 9–3	5.06	135.1	143.9	279.0
3–9	6.11	163.0	85.2	248.2
Night, 9–3	4.64	123.8	105.4	229.2
3–9	2.76	73.6	169.5	243.1
Total	18.6	495.5	504.0	999.5

Third Day of Ingestion.

Time of Day.	N in Urine.	Cal. from Protein.	Cal. from Fat.	Calories Total.
Day, 9–3	5.57	148.7	130.4	279.1
3–9	8.94	238.7	33.4	272.1
Night, 9–3	5.32	142.0	76.3	218.3
3–9	2.66	71.0	162.4	233.4
Total	22.5	600.4	402.5	1002.9

The nitrogen curve varies. The total heat production is greatest during the hours immediately following the ingestion of protein, but is otherwise comparatively even.

If we pass from the consideration of protein metabolism, as indicated by the nitrogen curve, to the consideration of the intermediary metabolism of protein we can see more clearly that the curve of protein nitrogen excretion is not a true index to the sum of the activities contributed to the cells by protein metabolism.

CHAPTER V.

THE INFLUENCE OF PROTEIN FOOD.

PART TWO.

The term "intermediary metabolism" with which so much modern work is intimately associated was used by Bidder and Schmidt on the first page of their celebrated "Verdauungssäfte und Stoffwechsel," published in 1852.

Voit[1] believed that there was an early cleavage of the protein molecule into a nitrogenous portion and a non-nitrogenous portion, a cleavage involving the liberation of only a small amount of energy; that there was a rapid combustion of the nitrogenous radicle, as shown by the elimination of the nitrogenous end-products in the urine; and that the non-nitrogenous radicle which contained the major part of the potential energy of the protein molecule might in part be temporarily stored either as glycogen or fat and be gradually doled out to the tissues as the need required.

Claude Bernard believed that glycogen could arise from protein. Wolffberg[2] let fowls fast two days to remove the glycogen and then for two days gave meat powder which was free from carbohydrate. Two fowls, killed during the interval of protein digestion, showed considerable glycogen in their livers (1.56 and 1.45 per cent.) and muscles (0.251 and 0.454 per cent.), much more than would have been present in starvation. Two similar fowls, killed seventeen and twenty-four hours after the last protein ingestion, contained much less

[1] Voit: "Zeitschrift für Biologie," 1891, Bd. xxviii, p. 291.

[2] Wolffberg: *Ibid.*, 1876, Bd. xii, p. 278.

glycogen in their livers (0.145 and 0.22 per cent.) and muscles (0.211 and 0.162 per cent.). This origin of glycogen from protein was fully confirmed by Külz[1] in a very extended series of experiments in which chopped meat, fully extracted with warm water, was made the basis of the ingesta. It became evident from these experiments that if sufficient protein were given to an animal, part of the protein carbon could be retained as glycogen.

It has long been believed that sugar arises from protein in diabetes. Kossel[2] first suggested that hexone bases, leucin, and other protein end-products, contained six atoms of carbon, as did also the ordinary hexose sugars, such as dextrose, levulose, and galactose. The theory of the origin of sugar in diabetes from these amino-products was strongly advocated by Friedrich Müller.[3] The definite proof of this was afforded by Stiles and Lusk,[4] who gave a mixture of amino-bodies prepared by the pancreatic proteolysis of meat to a dog rendered diabetic with phlorhizin. The mixture was free from protein. The nitrogen ingested was entirely eliminated in the urine, and for each gram of such nitrogen 2.4 grams of extra sugar appeared in the urine.

In the Chapter on Diabetes it will be shown how amino-acids of the general formula $C_nH_{2n}NH_2COOH$ may be deaminized with the formation of ammonia (which is convertible into urea in the liver) and organic oxyacids. The latter are either directly available for oxidation or they are wholly or in part convertible into dextrose, in which form they can be used by the organism. The heat value of protein lies in this *deaminized* or *denitrogenized* remainder. (See p. 163.) The earlier statements of Bidder and Schmidt (see p. 20) and of Voit (see p. 128) have therefore been fully justified, and it is right to believe that the true energy-yielding materials formed in the deamina-

[1] Külz: "Ludwig's Festschrift," 1890, p. 83.

[2] Kossel: "Deutsche medizinische Wochenschrift," 1898, p. 58.

[3] Müller and Seeman: *Ibid.*, 1899, p. 209.

[4] Stiles and Lusk: "American Journal of Physiology," 1903, vol. ix, p. 380.

tion of protein are like fat or carbohydrate in their value to the organism.

As regards the liver, even after severe artificial necrosis,[1] or the wide-spread action upon the cytoplasm of the parenchymatous cells which follows injection of hydrazin,[2] the urea-forming function still remains apparently undamaged. Jackson and Pearce point out that this is one of the many "factors of safety" in the body in the sense of Meltzer.[3]

Considerable sugar may originate from protein in the course of its ordinary metabolism. The question arises at what time during the metabolism does this sugar become available for combustion in the organism? This question was answered by an experiment of Reilly, Nolan, and Lusk.[4] These authors gave a fasting phlorhizinized dog 500 grams of meat and collected the urine in two three-hour and one six-hour period. The results were as follows:

EXCRETION OF DEXTROSE AND NITROGEN BEFORE AND AFTER INGESTING 500 GRAMS OF MEAT IN DIABETES.

	Dextrose.	Nitrogen.	D:N.
Preceding 3 hours	5.96	1.75	3.41
First 3 hours after feeding	12.43	2.52	4.92
Second 3 " " "	14.70	3.76	3.91
Third 3 " " "	11.23	3.85	2.92
Fourth 3 " " "	11.23	3.85	2.92
Following 3 hours	6.34	1.78	3.56

The normal fasting relation between dextrose and nitrogen changed immediately upon the ingestion of meat. During the first hours more dextrose was eliminated than corresponded to the nitrogen in the urine. During the later hours this proportion was reversed. The sugar elimination therefore took place decidedly before that of the nitrogen. This is shown in

[1] Jackson and Pearce: "Journal of Experimental Medicine," 1907, vol. ix, p. 552.

[2] Underhill and Kleiner: "Journal of Biological Chemistry," 1908, vol. iv, p. 165.

[3] Meltzer: "The Harvey Lectures," 1906–07, p. 139.

[4] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1898, vol. i, p. 395.

the following calculation of the percentage elimination of nitrogen and dextrose in three-hour periods following the ingestion of 500 grams of meat in the above experiment:

	Dextrose.	Nitrogen.
During first 3 hours	25.06	18.02
" second 3 "	29.64	26.90
" third 3 "	22.65	27.54
" fourth 3 "	22.65	27.54
	100.00	100.00

The relations are represented in the following curve:

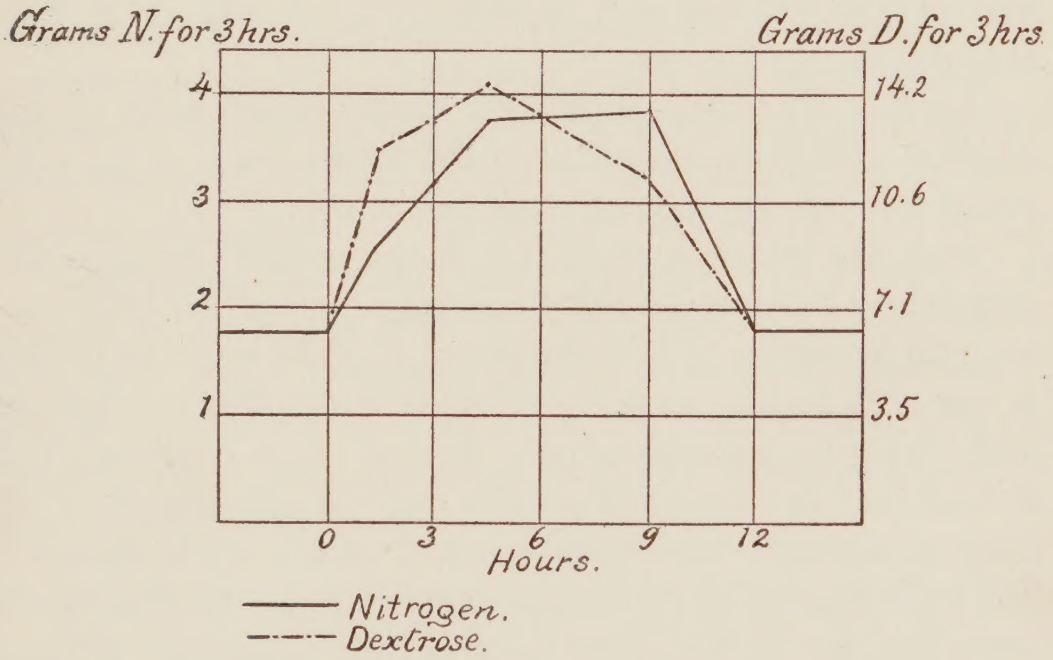


Fig. 7.—Curve showing the elimination of dextrose before nitrogen after meat ingestion (500 grams) in diabetes.

That the dextrose production from the meat ingested was proportional to the protein destroyed is evident from the following comparison, in which the sum of the dextrose and nitrogen eliminated in the twelve hours is considered. Nitrogen and dextrose double in quantity after the ingestion of meat, but their ratio remains the same as in starvation.

	Dextrose.	Nitrogen.	D:N.
Fasting 12 hours	23.87	7.00	3.41
After 500 g. meat, 12 hours	49.59	14.00	3.54
Subsequent 12 hours	25.36	7.11	3.56

The curve shows that there is an early production of sugar from protein which may be liberated in metabolism before the nitrogen belonging to the protein is eliminated in the urine. A similar early production of sugar from protein has also been observed after feeding dogs with meat in pancreas diabetes.[1]

Since one gram of nitrogen in the urine represents a destruction of 6.25 grams of meat protein, and since there is simultaneously an average elimination of 3.65 grams of dextrose in phlorhizin diabetes, it may be calculated that the sugar production from meat amounts to 58 per cent. by weight of the meat protein metabolized and may contain 52.5 per cent. of its total available energy (p. 70).

Another calculation shows that of the carbon from protein which is ordinarily eliminated in the respiration 63.2 per cent. passes through the dextrose stage (see p. 288).

After the ingestion of protein in the normal organism this sugar early becomes available and may be oxidized before the nitrogen belonging to it is eliminated, or if the sugar be formed in excess, it may be stored as glycogen in the liver and muscles of the body for subsequent use. In this way it is obvious that at least half the energy in protein may be independent of the curve of nitrogen elimination, but may rather act as though it had been ingested in the form of carbohydrate. Carbohydrates when ingested do not cause a rise in the production of heat, but may simply undergo oxidation as needed by the cells. This will be explained in the next chapter. It is therefore evident that this carbohydrate, which is early supplied in the breaking down of protein, may distribute its energy according to the requirement of the cells as long as it lasts. This is apparently the principal cause of the evenness of the carbon dioxid excretion as contrasted with the great irregularity of the nitrogen elimination after protein ingestion.

It has been noted that Frank and Trommsdorf, and Rubner

[1] Berger: Inaugural Dissertation, Halle (Nebelthau), 1901; cited from Maly's "Jahresbericht über Thierchemie," Bd. xxxi, p. 848.

also, in experiments previously mentioned, calculated the heat production during the first few hours after feeding with meat according to the usual method from the data furnished by the nitrogen and carbon elimination. This, however, will not tell the exact truth regarding the fat and protein metabolism during a short period, for dextrose from protein may be undergoing oxidation which is not indicated by the nitrogen excretion of the time. The error here introduced would not be large, but a correction would tend to reduce somewhat the calculated heat production during the period immediately following the ingestion of meat. This experiment should be controlled by simultaneous measurements with an animal calorimeter. It is obvious that respiration experiments extending over a few hours cannot so accurately present the picture of the metabolism after feeding with meat as they do in the case of starvation, where the intermediary metabolism is a constant and even factor.

Concerning the intermediate metabolism of protein, it is further shown by the work of Parker and Lusk[1] that the ingestion of casein by rabbits maintained under the influence of benzoic acid results in an elimination of hippuric acid which is proportional to the protein metabolism. This is illustrated in the following table:

CONSTANT RELATION BETWEEN GLYCOCOLL PRODUCTION AND N ELIMINATION AFTER INGESTING PROTEIN.

Day.	Casein Ingested in Grams.	Benzoic Acid given in Grams.	Grams Hippuric Acid Excreted.	Total N Excreted in Grams.	Hippuric Acid N: Total N.
First	4	1	.7230	1.469	1 : 25.9
Second	5	1	.7575	1.456	1 : 24.6
Third	10	1.5	1.0302	1.929	1 : 23.9

The total nitrogen and hippuric acid outputs maintain the same ratio throughout the above experiment.

It may be estimated that under these conditions the metabo-

[1] Parker and Lusk: "American Journal of Physiology," 1900, vol. iii, p. 472.

lism of protein within the organism yields 3.45 per cent. of glycocoll as compared with 3.98 per cent. obtained when body protein metabolizes in starvation (p. 71). This experiment seems remarkable because the chemist has not been able to obtain glycocoll from casein, and it may be quite possible that only a small part of the casein given was really digested and absorbed.

These results become very striking in the light of the work of Abderhalden, Gigon, and Strauss,[1] which shows that 100 grams of the protein matter composing the rabbits' body may yield 3.27 grams of glycocoll.

Magnus-Levy[2] finds that 25 to 27 per cent. of the total urinary nitrogen of rabbits fed with cream and of a goat fed with hay is excreted in the form of hippuric acid. He calculated that only 4 per cent. of this could have been derived from glycocoll preformed in the protein metabolized, but that 20 per cent. could have originated from leucin in passing through a glycocoll stage. Brugsch[3] finds that after the ingestion of benzoates in dogs and men not over three per cent. of the total nitrogen appears as hippuric acid, which is the equivalent of a production of 2.5 grams of glycocoll from protein. Why Parker and Lusk obtained the 4 per cent. elimination and Magnus-Levy secured one of 25 per cent. is not at present clear.

It has already been stated that the individual amino-acids lose their nitrogen at the first step in their metabolism. Only by union of its nitrogen atom with benzoic acid (see p. 71) is glycocoll spared this fate. One might believe that other amino-acids might unite with benzoic acid after a similar fashion and then be converted into hippuric acid by oxidation of the rest of their carbon chains. However, Magnus-Levy[4] found that

[1] Abderhalden, Gigon, and Strauss: "Zeitschrift für physiologische Chemie," 1907, li, p. 321.

[2] Magnus-Levy: "Münchener med. Wochenschrift," 1905, Bd. lii, p. 2168.

[3] Brugsch: "Centralblatt für Physiol. und Path. des Stoffwechsels," 1907, Bd. viii, p. 529.

[4] Magnus-Levy: "Biochemische Zeitschrift," 1907, vi, p. 541.

benzoylated compounds of alanin, valin, leucin, phenylalanin, aspartic acid, glutamic acid, orinthin, and serin when administered subcutaneously could not be changed into hippuric acid by the organism but were eliminated in the urine. No theoretical explanation can be given for the large quantity of hippuric acid which he found in goat's urine.

The writer unsuccessfully endeavored to bring about an elimination of cystin, the sulphur-containing compound in the protein complex, by constant treatment of a dog with benzol chlorid. The matter was then taken up by Wolf,[1] who has shown that after frequent administration of benzol bromid to a dog, an artificial cystinuria is brought about. The benzol bromid unites with the cystin liberated in protein metabolism and the compound, a mercapturic acid, is eliminated in the urine. In this way Wolf increased fourfold the unoxidized sulphur (cystin-S) in the urine, and nearly removed all the inorganic sulphate from the urine, although curiously enough there was a slight increase in the quantity of ethereal sulphates present. Folin and Alsberg[2] investigated a case of cystinuria and found similar relations. The increase in neutral sulphur was at the expense of alkaline sulphate in the urine. The cystin elimination was increased by increasing the protein in the food.

Thiele[3] has experimented on a cystinuric patient and finds the same quantity of cystin in the urine whether the patient be starving or fed with carbohydrates, with meat, or with the cystin which he has himself excreted. Since the cystin of meat and that obtained from his own excreta (which existing in his blood he could not burn) were nevertheless destroyed when ingested by way of mouth, Thiele argues that the seat of this destruction must have been the intestinal mucosa, to which locality modern theory more and more attributes the process of deamination (see p. 188).

[1] Mariott and Wolf: "American Medicine," 1905, vol. ix, p. 1026.

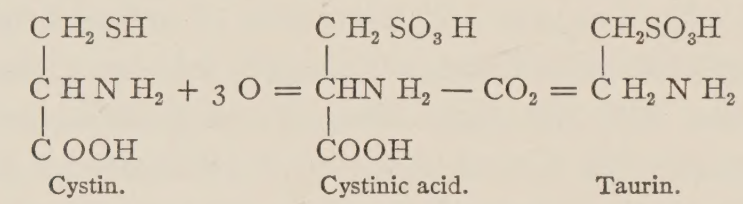
[2] Folin and Alsberg: "American Journal of Physiology," 1905, vol. xiv, p. 54.

[3] Thiele: "Journal of Physiology," 1907, xxxvi, p. 68.

Friedmann[1] shows that the cystin of mercapturic acid is the same cystin as may be obtained on the cleavage of protein in the laboratory.

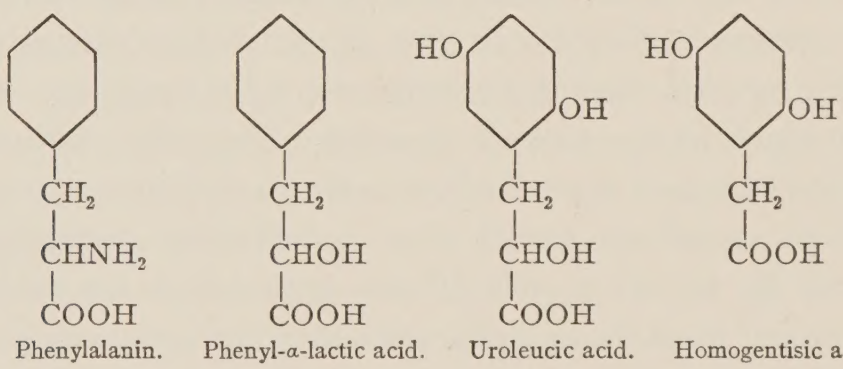
If cystin be administered to a normal person it is burned and does not alter the normal relation between oxidized and unoxidized sulphur in the urine.[2] Therefore cystin administered alone gives the same end-products as when it is administered in the protein complex.

That cystin is the mother substance of the taurin of the bile Friedmann[3] illustrates in accordance with the following formulæ:



The indications are that cystin is a normal product of protein metabolism which a patient suffering from cystinuria is unable to oxidize.

In a phenomenon called alcaptonuria tyrosin and phenylalanin are oxidized only as far as the alcaptonic acids, which are uroleucinic and homogentisic acids, and in this form they appear in the urine. Their production from phenylalanin according to Falta[4] is as follows:



He finds that if phenylalanin or tyrosin is administered in

[1] Friedmann: "Hofmeister's Beiträge," 1904, Bd. iv, p. 486.
[2] Blum: *Ibid.*, 1904, Bd. v, p. 1.
[3] Friedmann: *Ibid.*, 1902, Bd. iii, p. 1.
[4] Falta: "Biochemisches Centralblatt," 1904, Bd. iii, p. 175.

alcaptonuria, each is completely converted into the alcaptonic acids and so eliminated. In alcaptonuria the ratio between homogentisic acid and nitrogen elimination in the urine is constant, being 45 : 100,[1] while the distribution of the various other nitrogenous compounds in the urine remains normal. Garrod and Hale[2] find the same ratio as above, and believe with Falta that where this deviation from normal metabolism occurs it is complete in the sense that the homogentisic acid excreted represents the whole of the tyrosin and phenylalanin of the proteins broken down. For the normal fate of these substances see p. 293.

Neubauer and Falta[3] have recently emphasized the idea that the alcaptonic acids are always formed in normal metabolism, but in this rare disease cannot be further oxidized. The power to split the benzol ring is absent.[4]

Sugar, glycocoll, cystin, and the alcaptonic acids are therefore products of protein metabolism the excretion of which may be brought about by special means or by certain pathological conditions.

Kynurenic acid, which is regularly found in dogs' urine, has acquired new interest since Ellinger's[5] discovery that if a dog be given tryptophan—a product of proteolysis—the kynurenic acid is greatly increased in the urine. Mendel and Jackson[6] found that the kynurenic acid elimination in dogs varied directly with the protein metabolism, but was not derived from gelatin metabolism. Ellinger[7] has fed a rabbit, whose urine normally contains no kynurenic acid, with tryptophan, and found kynurenic acid in

[1] Langstein and Meyer: "Deutsches Archiv für klin. Med.," 1903, Bd. lxxviii; Schumm: "Münchener med. Wochenschrift, "1904, Bd. xxxvi, p. 1599.

[2] Garrod and Hale: "Journal of Physiology," 1905, vol. xxxiii, p. 205.

[3] Neubauer and Falta: "Zeitschrift für physiologische Chemie," 1904, Bd. xlii, p. 81.

[4] Neubauer: "Deutsches Archiv für klinische Medizin," 1909, Bd. xcv, p. 211.

[5] Ellinger: "Zeitschrift für Physiologische Chemie," 1904, Bd. xliii, p. 325.

[6] Mendel and Jackson: "American Journal of Physiology," 1898, vol. ii, p. 1. Consult also Mendel and Schneider: *Ibid.*, 1901, v, p. 427.

[7] Ellinger: *Loc. cit.*

the urine. Rabbits, however, normally burn kynurenic acid when ingested in small amounts. He reaches the conclusion that animals in general may produce kynurenic acid from tryptophan in protein metabolism, and that this is usually readily oxidized, except in the organism of the dog, where it is only partly destroyed and therefore appears in the urine.

The study of creatinin and creatin as excretory products has recently been stimulated by the discovery by Folin of a quick and relatively accurate method of determination.

He has given a diet of milk, cream, and carbohydrate which is free from creatinin and the purin bases, and has noted the effect of high and low protein content of the diet on the composition of human urine.

One of Folin's[1] experiments may thus be tabulated, percentages being rendered in black type (see Appendix, p. 364).

INFLUENCE OF HIGH AND LOW PROTEIN DIETS ON THE RELATIVE AMOUNTS OF THE NITROGENOUS CONSTITUENTS OF THE URINE.

Food.		Composition of the Urine in Grams.					
In Grams.	In Calories.	Total N.	Urea N.	Ammonia N.	Uric Acid N.	Creatinin N.	Undetermined N.
Protein, 118 = 19 N..... Fat, 148..... Carb., 225.....	2786	16.8	14.70 **87.5%**	0.49 **3.0%**	0.18 **1.1%**	0.58 **3.6%**	0.85 **4.9%**
Protein, 6 = 1 N.. Fat, 52..... Carb., 400.....	2153	3.6	2.20 **61.7%**	0.42 **11.3%**	0.09 **2.5%**	0.60 **17.2%**	0.27 **7.3%**

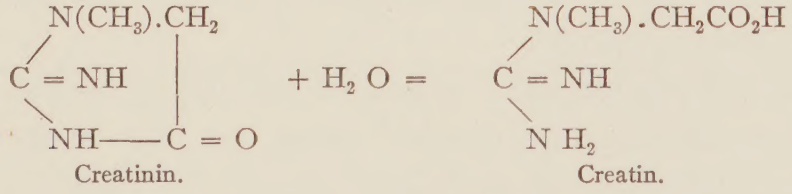
A study of this table will reveal the fact that if a man ingest a diet containing a medium amount of protein, and again one that is nearly free from protein, the difference in the character of the urine in the two cases is almost exclusively due to a difference in the output of urea. The quantity of creatinin

[1] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 117.

eliminated remains independent of the quantity of protein metabolized, and the same thing holds true as a rule for uric acid (see p. 344). This led Folin to distinguish between an *endogenous* protein metabolism which resulted in the constant and even production of creatinin and uric acid and was a manifestation of cell metabolism, and an *exogenous* protein metabolism as represented by the urea elimination which is in greater part derived from ingested protein.

The creatinin elimination is not influenced by muscular work[1] nor by the increased metabolism of body proteins which follows phosphorus poisoning in fasting dogs.[2] If creatinin be administered in the food it is largely eliminated in the urine.[3]

Fresh muscle substance contains creatin and never creatinin.[4] The production of creatinin from creatin has never been demonstrated, and the reverse reaction has lately been suggested. Mellanby finds that creatinin is not excreted by young chickens until one week after hatching, that is, not until after the muscles are saturated with creatin. Creatin is absent from the urines of young children.[5] The reason for this may be that the creatinin formed in metabolism is converted into creatin for the upbuilding of new tissue. Other investigators,[6] however, have found small quantities of creatinin in the urine of breast-fed infants during the first week of their lives. The chemical reaction would be as follows:



Creatinin. Creatin.

[1] Hoogenhuyze and Verploeg: "Zeitschrift für physiologische Chemie," 1905, vol. xlvi, p. 415.

[2] Lusk: "American Journal of Physiology," 1907, vol. xix, p. 461.

[3] Folin: "Hammarsten's Festschrift," 1906, iii, p. 10.

[4] Mellanby: "Journal of Physiology," 1908, vol. xxxvi, p. 447.

[5] Rietschel: "Jahrbuch für Kinderheilkunde," 1905, Bd. xli, p. 4.

[6] Amberg and Morrill: "Journal of Biological Chemistry," 1907, vol. iii, p. 311.

Normal urine never contains creatin. It is not a product of the endogenous metabolism. When ingested it may be destroyed or be eliminated in the urine, but is never converted into creatinin.[1]

In cases where body protein is metabolized, such as fasting, phosphorus poisoning,[2] carcinoma of the liver,[3] during the period of involution of the uterus after parturition[4] and also immediately before parturition,[5] creatin appears in the urine as an index of the breakdown of muscle tissue.

Mellanby concludes from the absence of creatin in the cross-striated muscle of the lobster that it is not essential either for muscle contraction or response to nerve impulses. He finds that muscular contraction is without influence on the creatin content of a muscle.

Much work and speculation have centered around the origin of creatinin without any certainty of result.

Creatin is the extractive existing in larger quantity than any other in muscle. In the process of manufacture of Liebig's extract of beef it is largely converted into creatinin. Such an extract, which contains also xanthin, is not strictly a food, since its constituents are largely ready for elimination in the urine.[6] Bürgi[7] shows that if meat extract be administered it is excreted in the urine excepting 4.57 per cent. of its nitrogen, 14.85 per cent. of its carbon, and 17.55 per cent. of its energy content.

Its value lies in its *flavor*, which promotes the proper flow of the digestive juices.[8]

It may be incidentally remarked that the principal value of many "patent" foods, "invalid" foods, etc., lies in their flavor.

[1] Folin: "Hammarsten's Festschrift," 1906, iii, p. 1.

[2] Lefmann: "Zeitschrift für physiologische Chemie," 1908, Bd. lvii, p. 476.

[3] Hoogenhuyze and Verploeg: *Ibid.*, 1908, Bd. lvii, p. 161. Also Mellanby, *loc. cit.*

[4] Shaffer: "American Journal of Physiology," 1908, vol. xxiii, p. 14.

[5] Murlin: "American Journal of Physiology," 1909, vol. xxiii, p. xxxi.

[6] Rubner: "Zeitschrift für Biologie," 1883, Bd. xix, p. 343.

[7] Bürgi: "Archiv für Hygiene," 1904, Bd. li, p. 1.

[8] Voit: "Stoffwechsel," 1882, p. 449.

If agreeable to the taste of the individual they usually afford a harmless indulgence. That beef, milk, cream, butter, and rice are equally suitable for all the purposes of proper living is a fact not sufficiently advertised. The old-time fraud of "patent" foods being "brain restorers" is as foolish a lie as can be written.

Rubner[1] says that the rise of the curve of sulphur elimination precedes that of nitrogen, while that of the phosphate elimination follows it. (See also p. 126.) The experiment is on the dog already described (page 127) during the six-hour periods following an ingestion of 460 grams of washed meat. The following represents the percentage elimination of nitrogen, sulphur, and phosphorus during six-hour intervals on the third feeding day. Of 100 per cent. there were excreted:

	N.	S.	P_2O_5.
During the first 6 hours.....	24.8	**36.7**	16.0
" second 6 "	**39.8**	31.7	32.1
" third 6 "	23.6	21.1	**33.4**
" fourth 6 "	11.8	10.5	18.5

Sherman and Hawk,[2] however, give curves showing beautifully an almost parallel elimination of sulphur and nitrogen in man on a mixed diet. A curve showing this is here presented:

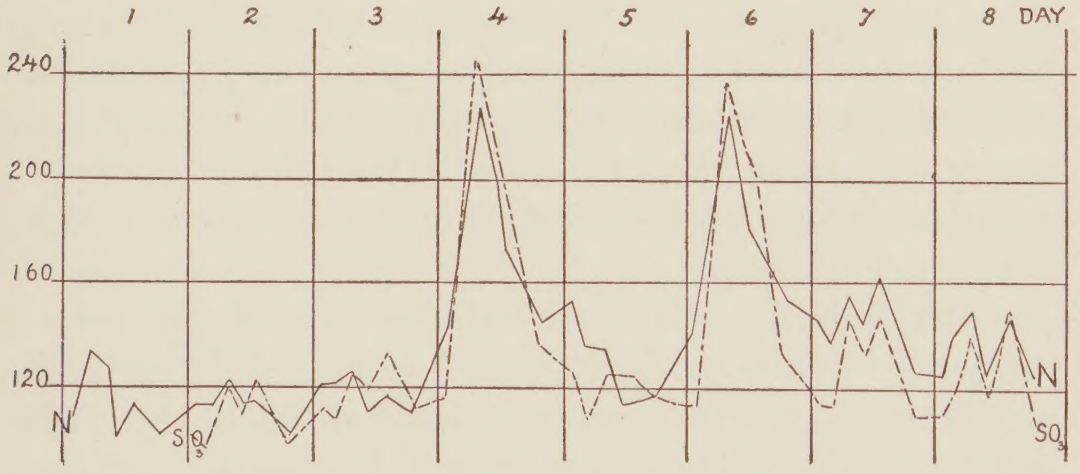


Fig. 8.—The curves here shown represent the relative fluctuations in the average rates of excretion of nitrogen and SO_3. The values on the left represent percentages of an assumed standard rate of excretion for each of these constituents. It will be seen that in general the excretion of sulphates ran quite closely parallel to that of nitrogen.

[1] Rubner: "Energiegesetze," 1902, p. 368.

[2] Sherman and Hawk: "Am. Jour. of Physiology," 1900, vol. iv, p. 43.

The parallelism of the hourly curves of nitrogen and sulphur excretion in man after the ingestion of veal cutlets is shown in the curve by Wolf on p. 125.

This discussion of the elimination of various intermediary products of protein metabolism lifts the mist from many factors sufficiently to give an outlook over a field of increasingly fruitful investigation.

A question which has aroused great interest is that concerning the production of fat from protein. Pettenkofer and Voit[1] found that after ingesting considerable quantities of protein, although the nitrogen of the protein was eliminated in the urine, a part of the carbon was retained in the body and not excreted by the usual channels. They estimated that meat protein contained 3.68 grams of carbon to each gram of nitrogen. If less than 3.68 grams of carbon appeared in the total excreta when one gram of nitrogen was eliminated, then some protein carbon must have been stored in the body. This carbon might have been retained in two forms—as glycogen or as fat. Claude Bernard had shown that glycogen increases in the liver after the ingestion of protein. The retained carbon as observed by Pettenkofer and Voit was in such large quantity as to preclude the possibility of its retention entirely as glycogen, and therefore they concluded that fat must have been prepared from protein and stored up in the body. This afforded an experimental basis for the theory of a production of fat from protein in fatty degeneration.

Later Rubner,[2] in Voit's laboratory, showed that the relation 3.68 C : 1 N in protein, as used by Pettenkofer and Voit, was inaccurate, and that meat fully extracted with ether contains only 3.28 of carbon to one of nitrogen. The polemical arraignment by Pflüger[3] of Voit's older work was based upon these

[1] Pettenkofer and Voit: "Annalen der Chemie und Pharm.," 1862, II Supplement, pp. 52 and 361.

[2] Rubner: "Zeitschrift für Biologie," 1885, Bd. xxi, p. 324.

[3] Pflüger: "Pflüger's Archiv," 1892, Bd. lii, p. 239.

results of Rubner. Instead of there being a great retention of protein carbon, there was none in some experiments and very little in others. The formation of fat from protein was evidently less easy of demonstration than it had seemed.

The subject was investigated anew by Cremer,[1] who starved a cat for many days, and then gave the animal all the lean meat it would eat, or about 450 grams a day. The cat was kept in a respiration apparatus and the total excreta were collected. The carbon belonging to the meat ingested was calculated at the low ratio of 3.18 to 1 of nitrogen. The average daily metabolism during the eight days of meat ingestion is indicated in the following table:

Weights in Grams.

N in urine and feces,	C in Urine,	C in Feces,	C in Respiration,	C in total,	Meat C calculated from N excreted,	C from meat added to the body,
13.0	7.5	1.4	25.4	34.3	41.6	7.3

There was a daily excretion of 13 grams of nitrogen corresponding to the liberation of 41.6 grams (13 × 3.18) of protein carbon. But only 34.3 grams of carbon were actually eliminated from the body, and a difference of 7.3 grams was retained in the body; 17.5 per cent. of the protein carbon therefore was not eliminated. For eight days the whole carbon retention was 58 grams, which corresponds to a glycogen production of 130 grams. The cat, however, contained only 35 grams of glycogen, determined after killing it at the end of the experiment. The balance of the carbon must have been stored as fat.

Cremer[2] notes that a cat fed as above contains 1.47 per cent. of muscle glycogen, which is as much as the maximum (1.37 per cent.) found by E. Voit in geese after the ingestion of starch.

Since it is known that sugar in excess may be converted into body fat and that meat may yield 58 per cent. of sugar in metabolism, there is every reason to believe that if protein be ingested

[1] Cremer: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 309.

[2] Cremer: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 313.

in excess this sugar may be converted into glycogen and then, if the quantity be sufficient, into fat.

It is quite possible that the origin of fat from protein is in its nature the same as the origin of fat from carbohydrates.

Rubner[1] has noted a similar carbon retention after the ingestion of protein in excess. Two examples of this may be cited.[2]

The first experiment was upon a dog which had been reduced by starvation from a weight of 11 to 6 kilograms. He was then given 500 grams of meat a day.

CARBON RETENTION AFTER PROTEIN INGESTION.

Day.	Food.	N in Excreta.	C from Fat Metabolism.	Calories from Protein.	Calories from Fat.	Total Cal. from Metabolism.	Body Weight.
First.....	Starvation.	1.31	22.46	32.75	275.2	308.0	5.94
Second....	Starvation.	1.52	19.77	38.00	243.2	281.2	5.82
Third.....	500 g. meat.	13.05	(—0.87)	339.3	—8.9	330.4	5.86
Fourth....	500 g. meat.	14.20	(—2.41)	355.0	—24.9	330.1	6.00

This experiment shows that on the first day of meat ingestion 0.87 gram of carbon from protein was retained in the dog and on the second day 2.41 grams were so retained. Rubner[3] has calculated that the carbon in the respiration derived from protein has a calorific value of 10.2 calories per gram. When protein carbon is retained in the body, its heat equivalent must be deducted from the heat value of the protein metabolism as computed from the nitrogen in the excreta, in order to obtain the true total of heat liberated. This heat value of retained carbon is a little above the calorific value of carbon in dextrose, which is 9.4 calories per gram.

The second experiment which may be cited was done by Rubner upon a large dog which was given 2000 grams of meat at a time. The results were as follows:

[1] Rubner: "Gesetze des Energieverbrauchs," 1902, pp. 57, 84.

[2] For a third example see this book, table on p. 151.

[3] Rubner: "Zeitschrift für Biologie," 1885, Bd. xxi, p. 363.

CARBON RETENTION AFTER PROTEIN INGESTION.

Day.	Food.			Excreta.		Calories.		
	Kind.	N.	Cal.	N.	Fat C.	Protein.	Fat.	Total.
First	Starv.			5.01	48.19	125.75	592.72	718.49
Second	Starv.			5.10	49.90	128.00	613.77	741.77
Third	2000 g. meat.	68	1926	51.60	(—29.58)	1351.9	—305.66	1046.34
Fourth	Starv.			12.39	37.19	325.62	420.54	746.16
Fifth	2000 g. meat.	68	1926	52.68	(—26.58)	1380.22	—274.57	1105.65
Sixth	Starv.			12.18	36.82	319.12	452.89	772.01

On both days when 2000 grams of meat were ingested, carbon was retained in the organism either as glycogen or fat. On the first of these days 17.7 per cent. of the total protein carbon was retained, which corresponds to 17.5 per cent. found by Cremer in the cat during a prolonged period of protein diet. The writer, on the basis of his work on diabetes, computes that 44 per cent. of the total carbon in meat protein may be converted into dextrose (p. 132). It is known that sugar is convertible into fat (p. 175). If 44 per cent. of protein carbon may be converted into dextrose, and under other conditions 17.5 per cent. may be converted into fat, it is evident that of the total dextrose-carbon which may be produced in protein metabolism, 40 per cent. can be converted into fat-carbon (p. 175). There seems to be no doubt that protein may in part be converted first into glycogen and then into fat after excessive protein ingestion.

An interesting contribution to this subject has been made by Weinland,[1] who found in the case of the blow-fly (*calliphora*), which lays its eggs in meat, that both the larvæ and a pulp made by crushing them had the power, in the absence of oxygen, to split peptone into amino-acids, deaminize these with evolution of ammonia, and then with evolution of carbon dioxid to produce higher fatty acids, presumably through synthetic union of the acids which had been freed of their amino groups. Such a

[1] Weinland: "Zeitschrift für Biologie," 1908, Bd. li, p. 197.

procedure reasonably explains the formation of fat from protein in the sense of the older theories. (See p. 128.)

The question of a "fatty degeneration" of protein under pathological conditions is another matter and will be considered in another place. (See Chapter XII.)

The last two experiments of Rubner's bring to light a very striking change in the metabolism after the ingestion of protein in excess. The total heat production is markedly increased. To what may this be due?

Von Mering and Zuntz[1] believed that such increased metabolism was due to the activity of the intestinal tract after the ingestion of food.

Voit[2] criticized this view and said that a rise in the carbon dioxid excretion, from 366 grams in starvation to 783 grams after ingestion of meat in excess, was too great to be due to intestinal activity, and, indeed, corresponded to the rise noted only after the hardest exercise. Furthermore, Voit had shown that after giving a medium quantity of fat, the carbon dioxid excretion and oxygen absorption were almost the same as in hunger, notwithstanding the activity of the filled intestine.

This question has received very painstaking and elaborate investigation at the hands of Rubner, who has published his results in a book entitled "Die Gesetze des Energieverbrauchs bei der Ernährung." This volume is an extension of a work of which a preliminary communication was published by Rubner[3] from Voit's Munich laboratory in 1885. During subsequent years of continued activity the doctrines were more and more firmly established.

Rubner shows that bones given to a dog will not increase his metabolism, in spite of the intestinal irritation, so the increase after meat ingestion is not due to a nerve reflex of mechanical

[1] von Mering and Zuntz: "Pflüger's Archiv," 1877, Bd. xv, p. 634.

[2] Voit: "Physiologie des Stoffwechsels," 1881, p. 209.

[3] Rubner: "Sitzungsberichte d. kgl. bayr. Acad. d. Wissenschaft," 1885, Heft 4.

nature. Further, the metabolism is not raised after the ingestion of meat extract, so the chemical stimulus of flavors which start activity in the glands does not affect total metabolism. Again, the ingestion of water in the quantity contained in meat, while it may cause a rise in nitrogen in the urine followed by a fall—the rise being due to a rapid washing out of nitrogenous decomposition products—does not alter the total metabolism in any way.

The absence of true "intestinal work" or "Darmarbeit" in the sense of Zuntz is further shown by the fact that Johansson[1] has given a fasting man 75 grams of dextrose without the slightest increase in the output of carbon dioxid. If dextrose had been consumed the carbon dioxid excretion would have risen (see p. 176), therefore dextrose was retained as glycogen. Since all these processes were without effect on the carbon dioxid output it follows that the intestinal activities involved did not cause an increase in the total metabolism. Of similar import are the results by the same writer after administering 50 grams of dextrose to a diabetic. The sugar was absorbed and eliminated in the urine without affecting the carbon dioxid output.

Cohnheim[2] has employed "fictitious feeding" in a case of a fasting dog with an esophageal fistula. The dog was given meat which passed through the fistula without reaching the stomach. Such a procedure results in a psychic flow of gastric juice, which in turn starts up activity in the digestive glands of the intestinal tract. The result showed an increased heat production of 9 per cent. during a three-hour period. The animal had been kept at an environmental temperature of 33°. There was no increase in the protein metabolism and the "intestinal work" was therefore accomplished at the expense of the fat or glycogen reserve. Cohnheim notes that if the above increase in metabolism were distributed over twenty-four hours it would amount to only 1 per cent. of the total energy production, and would

[1] Johansson: "Skandin. Archiv für Physiologie," 1908, Bd. xxi, p. 1.
[2] Cohnheim: "Archiv für Hygiene," 1906, Bd. lvii, p. 401.

not explain the very great increases in metabolism which have been noted after the ingestion of meat in large quantities.

Rubner determined the starvation metabolism during twenty-four hours and used this as a unit for the measurement of the absolute "requirement" of the organism. This "requirement" of energy may be met by the ingestion of an equivalent "maintenance diet" which covers the requirement. An "abundant diet" contains a larger amount of potential energy than the organism requires.

Rubner at first found that if the food ingested had a lower calorific value than the body's requirement, then the metabolism was not usually increased after the ingestion. This is illustrated in one of his earlier experiments[1] summarized below.

Food.	Metabolism in Calories.
Starvation	867
Bones, 40 grams	812
Meat, 720 grams	836
Meat, 760 grams	875

So if the food contains less than the energy requirement, the metabolism may not be increased in spite of activity of the glands and muscles of the intestinal tract.

To explain this Rubner[2] introduced his *compensation theory*. This assumed a certain reciprocity between the muscles and the glands. During starvation and medium temperature, a great part of the body's heat is produced in the muscles, and those cells ordinarily concerned in taking up food are quiet and produce little heat. On warming the outside air the amount of metabolism in the muscles decreases. The same thing may take place when gland cells and intestinal musculature are thrown into activity; the voluntary muscles are proportionally relieved from the necessity of heat production for the maintenance of body temperature through chemical regulation.

Quite a different picture is presented when an abundant diet is supplied to the dog. If protein above the calorific re-

[1] Rubner: "Zeitschrift für Biologie," 1883, Bd. xix, p. 349.

[2] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 8.

quirement be ingested there is a very considerable rise in the heat production. This increase is greater in the case of protein than with any other foodstuff. Rubner calls this action of abundant protein food in raising the metabolism the *specific dynamic* action of protein. This action is shown in the two experiments of Rubner cited on pages 144, 145. In the second experiment, the total metabolism during the starvation days is as follows:

First day	718.5 calories.
Second day	741.8 "
Third day	746.2 "
Fourth day	772.0 "

Rubner took the average of the last two days as representing the requirement in starvation, or 759.1 calories. After administering 2000 grams of meat containing 1962 calories, or the full starvation requirement and 153.7 per cent. besides, the heat production rose from 759.1 calories per day to 1046.34 and 1105.65 calories,—that is, it increased 42.2 and 45.6 per cent. Rubner recalculated the calories produced by the metabolism during the experiment on the assumption that the carbon from protein was retained as glycogen and not as fat, and in this way estimated the increased metabolism after this ingestion of meat at 45.5 and 48.7 per cent. above the starvation minimum.

Combining the results of such experiments, Rubner[1] finds the following increasing specific dynamic effect of protein as the quantity above the day's requirement becomes larger.

Excess above Requirement.	Increase in Heat Production.
56 per cent.	19 per cent.
90 "	35 "
105 "	44 "
153 "	49 "

Here were increases in total metabolism comparable to those induced by considerable mechanical work. The body metabo-

[1] Rubner: "Gesetze des Energieverbrauchs," p. 90.

lized in largely increased measure without doing any external work.

A more rapid respiration alone betokened the increased oxidation and the effort of the body to rid itself of excess of heat through physical regulation. The temperature of the dogs scarcely changed, so perfect is the regulatory mechanism for the discharge of heat. Thus in one dog the temperature was 38.16° before the meal, 38.74° during the digestion, and 38.17° at the end of digestion.

Rubner differentiated between three stages of protein metabolism. *First*, in the cases of undernutrition and of maintenance diet in which protein enters into the circulation and spares an isodynamic quantity of the body substances; *second*, the stage of abundant nutrition where the protein raises the metabolism through its specific dynamic power; *third*, an intermediary stage where protein may be added as tissue to the body without increasing the metabolism. This period of "pure deposit" of tissue may rapidly pass into the stage of deposit united with specific action causing increase in heat production. It will be apparent later that the first and third stages of protein nutrition can be achieved only at low or medium temperatures of environment.

An example of the stage of the deposit of protein tissue without a rise in metabolism is given by Rubner[1] as follows:

	N to Body.	Calories per Kg.
Starvation	——	45.61
Starvation	——	43.26
Meat	+ 8.7	44.48
Meat	+ 4.7	46.16

This kind of growth of tissue without a corresponding rise in metabolism takes place in the normal adult only when the protein ingested is below the heat value of the fasting metabolism. If, however, a larger quantity of protein be ingested than

[1] Rubner: "Gesetze des Energieverbrauchs," p. 256.

the heat requirement of the body calls for, then the usual specific dynamic action occurs and also a continued "secondary" rise in total day-to-day metabolism, which increases as long as protein is deposited. When nitrogen equilibrium is established the heat production remains constant at a higher level.

Rubner[1] illustrates this important fact in the following experiment on a dog:

Calories in Meat Ingested.	N to Body.	Carbon to Body.	Total Calories of Metabolism.
0	—1.31	. . .	310.61
0	—1.52	. . .	278.00
481.5	3.95	2.97	311.43
481.5	2.80	3.70	333.82
481.5	2.30	1.61	368.41
481.5	2.20	2.53	361.70
481.5	0.92	4.45	375.47
481.5	0.20	4.31	395.77
0	—3.70	. . .	357.20
0	—2.64	. . .	310.29

The constant deposit of protein therefore continually raises the heat production in the organism until a point is reached when no more protein is added to the body. This is the point of nitrogenous equilibrium, and is very quickly attained. It is evident that on a purely protein diet no great addition of protein tissue can usually take place in the adult on account of this *secondary dynamic action.* (Compare with Bornstein's work, p. 110.)

Rubner shows that the retention of fat from protein in the body has nothing to do with this action. Protein retention is much more readily brought about on a mixed diet containing large quantities of carbohydrates, as will be seen in a subsequent chapter.

Thus far in this book the influence of external temperature upon the course of protein metabolism has not been discussed. Rubner has shown that this is a factor of profound significance. It has already been demonstrated how, through

[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 246.

chemical regulation, the basal requirement of the body is reflexly increased by increasing cold in the environment. Rubner[1] compared the starving metabolism of a dog at different temperatures with that of the same dog when 100, 200, and 320 grams of meat were ingested. The results are presented as follows in terms of calories produced per kilogram of body weight:

INFLUENCE OF EXTERNAL TEMPERATURE ON METABOLISM AFTER PROTEIN INGESTION.

Temperature.	Starvation.	100 Gm. Meat or 24 Cal. per Kg.	200 Gm. Meat or 48 Cal. per Kg.	320 Gm. Meat or 81 Cal. per Kg.
7°	86.4	....	77.7	87.9
15°	63.0	....	....	86.6
20°	55.9	55.9	57.9	76.3
25°	54.2	55.5	64.9	....
30°	56.2	55.6	63.4	83.0

One hundred grams of meat did not change the metabolism at 20°, 25°, or 30°; 200 grams of meat had no effect at 20° or at 7°, but at 25° and at 30° there was an increase, although the food contained fewer calories than the requirement. With 320 grams of meat there was a great increase above the starvation requirement, except at 7°, where it is a maintenance diet and the metabolism remains unchanged. In other words at a temperature of 30° the specific dynamic action of this amount of protein is capable of increasing the heat production above that of starvation by about 53 per cent., while at 7° there is no change whatever. It is also evident that at a high temperature even a small quantity of protein such as 200 grams of meat causes a considerable rise of metabolism.

Rubner gives the metabolism in terms of calories per kilogram after the ingestion of 550 grams of meat or 173.8 calories per kilogram of body weight in a dog, as follows:

[1] Rubner: *Ibid.*, p. 109.

Temperature.	Starvation.	550 Grams Meat.	Increase.
4.2°	128.1	133.5	4.2 per cent.
14.5°	100.9	110.9	9.9 "
22.1°	70.7	101.0	42.9 "
30.7°	62.0	117.2	89.0 "

These experiments make evident the extraordinary influence of variations in the surrounding temperature on the metabolism when the same quantity of meat is given. The influence of temperature must therefore be continually kept in mind as a most important factor of the amount of the metabolism. Many experiments reported as having been done at the "room temperature" have an indefinite value.

An additional point of interest is that in certain cases the intensity of the metabolism remains constant throughout the experiment, notwithstanding a variation in the temperature. This is shown on p. 152, where the dog was given 320 grams of meat. The amount of the metabolism scarcely varied with the temperature. The chemical regulation, or the increased heat production brought about by a reduction of the surrounding temperature, is not evident in this case. Here the fuel value of the food was equal to the requirement of the body even at a temperature of 7°.

From the general results of these experiments Rubner[1] deduces two important laws which govern metabolism as influenced by temperature. Their significance will be better appreciated in the analysis of the subject in the following chapter.

"The first law is that, within limits normally compatible with life, warm-blooded animals are capable of adapting themselves to change in external temperature through a reflex increase or decrease of the activity of their heat-producing apparatus. For every state of body substance and for every temperature of the environment there is a definite amount of heat loss to which the organism—with the aid of its heat-regulating apparatus—tends to approach. This may be called the minimal heat requirement.

[1] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 160.

There is no law enforced with greater severity or fatality. The starving man who lives on his own substance cannot remove himself from its influence. Inexorable until the last hour of life it demands fulfilment. . . . . It kills the starving child in days, while it allows the starving adult weeks."

"The second law concerning the relation of external temperature to the organism is: *The mechanism of the physical regulation of body temperature can never enter as a factor until the heat production equals the requirement of the organism. If, however, the heat production be greater than corresponds to the minimal requirement for that temperature, then the heat production within certain limits becomes independent of the temperature. Under these circumstances the heat production does not decrease on raising the external temperature, and only increases when through increasing cold the former heat production no longer covers the minimal requirement of the organism for heat.*"

This second law explains why in certain cases after food ingestion the carbon dioxid excretion may remain constant at different temperatures of environment. Its action is seen in the dog mentioned on page 152, after he had eaten 320 grams of meat at various room temperatures. The increase in body metabolism due to the stimulus of cold (chemical regulation) is not necessary, since heat in excess of the requirement is already available. All that is needed is the arrangement of avenues of escape for the excess of heat produced from the food ingested (physical regulation). This physical regulation is brought about by the evaporation of water and by a change in the distribution of the blood.

How the increased evaporation of water enters as a refrigerating factor is beautifully shown in the experiment on the dog (p. 152) which fasted and then received 100, 200, and 320 grams of meat at various room temperatures. The distribution of the loss of heat by radiation and conduction and by the evaporation of water was as follows:

DISTRIBUTION OF HEAT LOSS FROM A DOG AFTER MEAT INGESTION.

Temperature.	Hunger.		100 Grams Meat.		200 Grams Meat.		320 Grams Meat.	
	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.	Cal. from Radiation and Conduction.	Cal. from Evaporation of Water.
7°	78.5	7.9	- - -	- - -	67.1	10.6	78.5	9.4
15°	55.3	7.7	- - -	- - -	46.7	11.2	76.2	10.4
20°	45.3	10.6	46.7	9.2	49.5	15.4	- - -	- - -
25°	41.0	13.2	- - -	- - -	- - -	- - -	- - -	- - -
30°	33.2	23.0	34.1	21.5	27.8	35.6	34.5	48.5

It is evident from the above that the greater part of the loss of heat at a low temperature was by radiation and conduction, but at a high temperature (30°) the loss by the evaporation of water was largely increased. The extra heat production on account of the specific dynamic action of the protein, was lost through the increased evaporation of water.

Much meat on a hot day would therefore seem contraindicated.

While the chemical regulation protects the body from an abnormal fall in temperature, the physical regulation prevents an abnormal rise in temperature. The organism may be at times under the influence of one means of regulation, at times of the other, and without being conscious of any difference.

Cold-blooded animals have no chemical regulation, and their temperature falls with that of their surroundings.

The following chapter will more fully discuss the cause of the specific dynamic action of the foodstuffs.

CHAPTER VI.

THE SPECIFIC DYNAMIC ACTION OF THE FOODSTUFFS.

A study of the specific dynamic action of protein in its relation to temperature changes gave Rubner[1] new points of view. He saw (experiment on p. 152) that by chemical regulation the metabolism in a fasting dog was increased from 54 to 86 calories per kilogram, an increment of 32. And he likewise observed that after the ingestion of 320 grams of meat the heat produced at a room temperature of 30° rose from 56 in starvation to 83, a difference of 27 calories. The source of the increase through chemical regulation is known to be chiefly in the muscles. The increase brought about by protein ingestion had been shown by Rubner to be due not to any such thing as intestinal activity (Darmarbeit), but rather to some specific heat-raising effect of protein metabolism itself. It was apparent that these two sources of increased heat might enter into a reciprocal arrangement because on cooling the atmosphere in which the dog lived to 7° C., the metabolism, after the ingestion of 320 grams of meat, remained at 87.9 calories in contrast with 83.0 on feeding at 30°. Here the heat due to the specific dynamic action was used in replacement of that induced by chemical regulation. This illustrates Rubner's modified idea of his *compensation theory*, or a reciprocity between heat produced in the muscles by chemical regulation and the extra heat production brought about through the ingestion of food.

Since the extra heat production after food ingestion could be utilized instead of heat from chemical regulation, Rubner perceived that the true increase through specific dynamic action could be measured only at the temperature of 33°, where there was no reflex increase in metabolism through chemical regulation.

[1] Rubner: "Energiegesetze," p. 145.

It was especially important to make experiments regarding the action of foodstuffs at a temperature of 33°, for that is the temperature with which man surrounds his skin. By means of clothes and artificial heating man constantly tries to remove himself from the influence of chemical regulation. His daily life is practically under the influence of a tropical climate. His metabolism is unchanged from the normal when he is immersed in a bath at 33°.[1]

Rubner therefore planned an experiment in which a dog was kept at a temperature of 33°. At times the animal was made to fast in order that the basal requirement could be determined, and during other definite periods, meat, fat, and carbohydrates, either alone or combined, were ingested, and the increased metabolism due to the varying dietaries was noticed. The experiment extended over a period of forty-six days.

A summary of the results obtained is shown in the following table and is graphically illustrated by the accompanying figure 9, which has been taken from Rubner.[2]

TABLE INDICATING THE SPECIFIC DYNAMIC ACTION OF DIFFERENT FOODSTUFFS AT 33°.

VALUES IN CALORIES PER KILOGRAM BODY WEIGHT.

DIET-*	HUNGER REQUIREMENT.	FOOD INGESTED.	PROTEIN INGESTED.	METABOLISM.	INCREASE ABOVE HUNGER IN PER CENT.
100 per cent. fat	54.0	53.4	- - -	60.9	12.7
66 per cent. meat	53.5	37.7	32.3	62.1	16.0
10 per cent. meat 90 per cent. fat	53.4	55.5	5.1	60.6	13.4
20 per cent. meat 80 per cent. fat	52.5	59.3	10.5	63.6	21.5
100 per cent. meat	52.0	63.0	57.1	73.8	41.9
Meat, fat, sugar	51.0	59.8	8.8	55.6	9.0
100 per cent. meat	51.0	60.3	56.3	67.3	31.9
Meat, fat, starch	50.0	48.0	8.1	52.0	4.0
87 per cent. sugar	50.0	43.6	- - -	52.5	5.0
66 per cent. meat	50.0	34.5	31.6	60.4	20.8

* Percentages are in terms of the starvation requirement and are approximate only.

[1] Rubner: "Archiv für Hygiene," 1903, Bd. xlvi, p. 390.

[2] Rubner: "Energiegesetze," p. 324.

It is clearly evident that meat ingestion raises the metabolism most, fat next, and sugar least of all the foodstuffs. The ingestion of the starvation requirement for energy in the form of fat raises the metabolism 12.7 per cent. During the two periods when approximately 100 per cent. of the basal requirement was ingested as meat there was an *average increase* in the metabolism of 36.7 per cent.

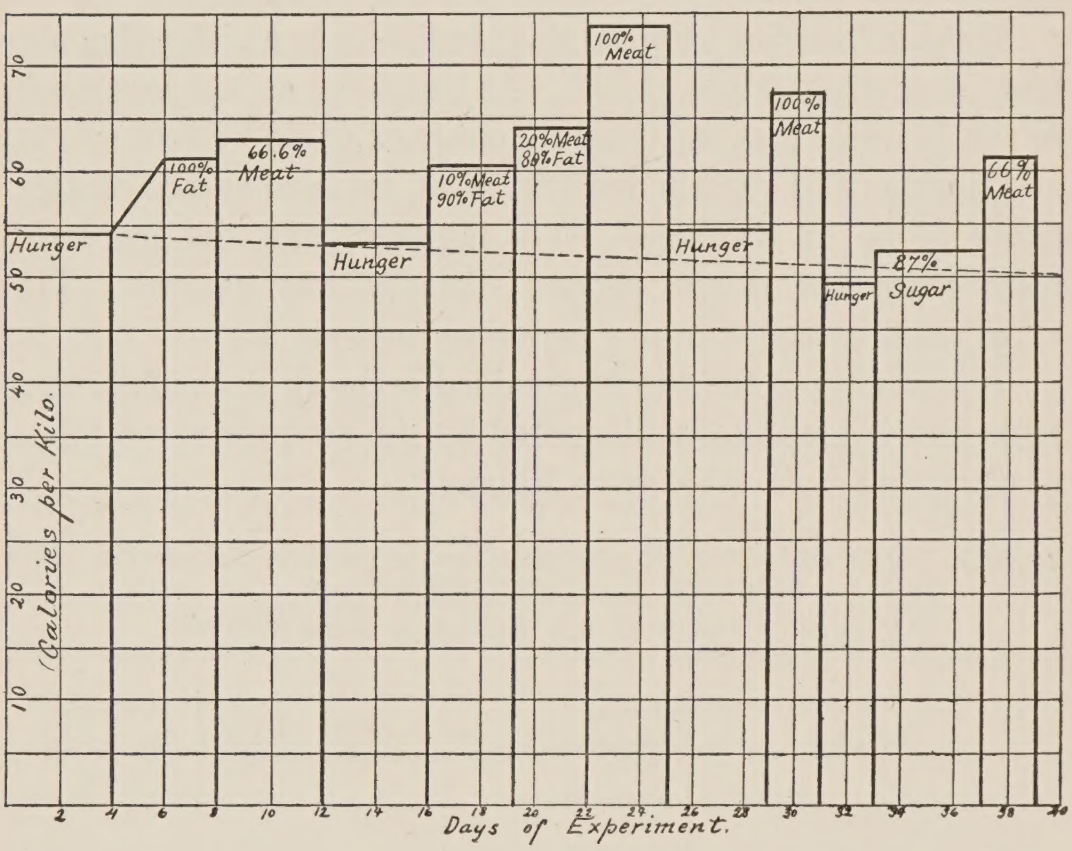


Fig. 9.—Rubner's chart indicating the specific dynamic action of different foodstuffs ingested at a room temperature of 33°. The dotted line indicates the height of the fasting metabolism.

More detailed examination, however, reveals the fact that the exact quantity of meat ingested contained 119.6 per cent. of the basal requirement of calories, of which 110.1 were contained in meat protein and the balance in fat present in the meat. If under the influence of the ingestion of 119.6 per cent. of the basal requirement the metabolism rose 36.7 per cent., then the increase due to the ingestion of 100 per cent. would have been

30.74 per cent. But this meat containing 100 per cent. of the basal requirement in reality consisted of meat protein containing 92.06 per cent. of the energy and of fat containing the remaining 7.94 per cent. Since the ingestion of fat sufficient to provide 100 per cent. of the basal requirement for energy raises metabolism 12.7 per cent., then fat sufficient to provide 7.94 per cent. of the basal requirement must increase metabolism 7.94×0.127 or 1.01 per cent.

Deducting this 1.01 per cent. which is due to the specific dynamic action of the fat ingestion from the total increase of 30.74 per cent., it is found that 29.73 per cent. increase is due to the 92.06 per cent. of pure meat protein ingested.

If 92.06 per cent. of meat protein raises the metabolism 29.73 per cent., then 100 per cent. of such protein will increase it by 32.28 per cent. Using the same procedure in computing the heat-raising power of two-thirds the basal requirement of energy for the dog, ingested in the form of meat, it was calculated that if 100 per cent. of the requirement had been the quantity supplied the increase in the metabolism would have been 29.60 per cent. Rubner therefore found that—

I. After ingesting meat in excess of the starvation metabolism, the specific dynamic action caused a heat increase of 32.28 per cent.

II. After ingestion of a quantity smaller than that of the starvation metabolism the specific dynamic action similarly measured was 29.60 per cent.

The average of these, or 30.94 per cent., represents the specific dynamic action of protein or the increased heat production after the ingestion of meat containing 100 per cent. of the energy requirement, when the animal is outside of the influence of the chemical regulation.

In another case, after the ingestion of meat in large excess, Rubner finds the increase due to the specific dynamic action to be 32.2 per cent. The action of gelatin is similar, the increase

in metabolism being 28.0 per cent. for every 100 calories in the gelatin ingested.

Again Rubner[1] has determined the amount of the metabolism of a fasting dog and that of the same dog made diabetic with phlorhizin (see p. 287). Under the latter circumstances the protein metabolism is greatly increased. He found that for every 100 calories increase in body protein broken down there was an increased heat production of 31.9 calories. Here was a rise in heat production not due to protein ingestion and therefore not due to intestinal work, but due to the mere fact of increased protein metabolism in starvation. The specific dynamic action of protein then may thus be tabulated:

	Increased Heat Production for every 100 Calories Ingested or Metabolized.
Meat protein	30.9
Gelatin	28.0
Body protein (phlorhizin diabetes)	31.9

It has furthermore been shown by Falta, Grote, and Staehelin[2] that casein and the amino-acids resulting from the hydrolysis of casein when given to a dog exert the same specific dynamic action as do the proteins of meat.

Regarding cane sugar, the experiment shows that after its ingestion to the extent of providing 86.41 per cent. of the starvation requirement for energy, the metabolism increased only 5 per cent. It may be calculated that if 100 per cent. of the basal requirement had been given the increase would have been 5.8 per cent.

Summarizing, it is evident that if the same quantity of energy be contained in the ingested food as the body requires in starvation at a temperature of 33° C., there will be the following increases in heat production:

Protein	30.9 per cent.
Fat	12.7 per cent.
Cane sugar	5.8 per cent.

[1] Rubner: "Energiegesetze," p. 370.

[2] Falta, Grote, and Staehelin: "Hofmeister's Beiträge," 1907, Bd. ix, p. 334.

Food equal to the basal requirement of energy in starvation at the temperature of 33° cannot therefore maintain the body in calorific equilibrium. Rubner, however, calculates the following as the minima of ingestion for the three foodstuffs, when the hunger minimum is 100:

Hunger minimum	100
Protein "	140.2
Fat "	114.5
Cane sugar minimum	106.4

In other words, if 100 calories be the starvation requirement, 140 calories must be supplied if calorific equilibrium is to be maintained by the ingestion of protein alone; whereas in the case of sugar, 106.4 calories are all that are required to prevent the loss of energy content from the body's material. That these results are not limited in their application is shown by Rubner's[1] experiment on a man who was given 120 per cent. of the starvation requirement of energy first in the form of sugar and then of meat. The metabolism was as follows:

Starvation	2042 calories in 24 hours.
Sugar alone	2087 " " " "
Meat alone	2566 " " " "

As neither man nor dog ever lives on meat alone except under forced feeding, the results are not usually so pronounced as in the above case. Average dietaries, according to Rubner,[2] show the following distribution of percentage of calories:

PERCENTAGE OF CALORIES IN DIFFERENT DIETS.

	Protein.	Fat.	Carbohydrates.
I.—Well-to-do individual	19.2	29.8	51.0
II.—Workman	16.7	16.3	66.9
III.—Exceptional cases	8.3	38.7	52.8

It is possible to calculate the specific dynamic effect of such diets by multiplying the quantities of foodstuffs by their specific dynamic factor,—for example, 100 per cent. of protein = 30.9 per cent. increase; 1 per cent. = 0.309 per cent. increase, and

[1] Rubner: "Energiegesetze," p. 410.

[2] Rubner: *Ibid.*, p. 415.

therefore 19.2 per cent. protein in the food must cause an increase of 0.309 × 19.2 = 5.93 per cent. in the metabolism due to the ingestion of protein in Diet I.

Calculating the diets as above, the following figures are obtained:

I.	Protein	19.2 × 0.309	=	5.93
	Fat	29.8 × 0.127	=	3.77
	Carbohydrate	51.0 × 0.058	=	2.96
			+	12.66 per cent.
II.	Protein	16.7 × 0.309	=	5.15
	Fat	16.3 × 0.127	=	2.06
	Carbohydrate	66.9 × 0.058	=	3.88
			+	11.09 per cent.
III.	Protein	8.3 × 0.309	=	2.56
	Fat	38.7 × 0.127	=	4.91
	Carbohydrate	52.8 × 0.058	=	3.06
			+	10.53 per cent.

Thus, if the starvation requirement for energy be ingested the increase in metabolism would be:

Diet	I	12.66 per cent.
"	II	11.09 "
"	III	10.52 "

and from this it may be calculated that calorific equilibrium would be reached by ingesting the following increases above the starvation requirement:

Diet	I	14.4 per cent.
"	II	12.4 "
"	III	11.1 "

On an average mixed diet the ingestion minimum is therefore between 11.1 *and* 14.4 *per cent. above the starvation requirement. This would be the maintenance requirement.* (Rubner.)

Should the fasting metabolism of a man be 2400 calories, the ingestion of food would act as follows:

	Diet I. (19.2% protein)	Diet III. (8.3% protein)
After ingestion of starvation requirement of energy	2703	2652
After ingestion of maintenance minimum	2745	2666

That mixtures of the foodstuffs do act nearly after this fashion Rubner has proved.

On account of the great specific dynamic action of protein, Rubner would restrict its use in fever and substitute carbohydrates as the source of energy.

During the heated term of midsummer, diminution of protein ingestion will materially improve the personal comfort by decreasing the heat production and the consequent necessity for sweat production (p. 217).

As to the cause of the specific dynamic action, Rubner offers this theory: The cells of an organism require a fixed quantity of potential energy which must be furnished to them in metabolizable compounds. This quantity is the same for all temperatures and free heat cannot be employed for this purpose. The value of the foodstuffs depends upon the potential energy they can give to the cells. If cane sugar is ingested, for example, 3.1 per cent. of its energy is dissipated as heat when it is inverted into levulose and dextrose. This heat cannot be used for the life processes in the cells. When protein breaks up in metabolism, large quantities of sugar are produced. According to Rubner, this earlier metabolism of protein yields heat, but not energy for the cells. He thinks that the protein sugar and possibly other cleavage compounds may in this case be the true source of power for the living mechanism. The extra heat of the earlier process which is wasted when the environment has a temperature of 33°, may however be used as a substitute in the place of the heat which may be required by chemical regulation. Here heat and not potential energy is required. Bearing these considerations in mind, foodstuffs are replaceable in accordance with their respective energy equivalents.

The theory may be schematically indicated as follows:

STARVATION REQUIREMENT OF POTENTIAL ENERGY BY CELLS = 100 CALORIES.
140 Calories in Protein of Meat Ingested.

40 Calories = free heat liberated in early cleavage, available in replacement of heat of chemical regulation.	100 Calories = Potential energy from protein available for cell life.

From this it may be calculated that when protein is metabolized 71.4 per cent. of its energy content is available for cell life, while 28.6 per cent. is liberated as free heat. It has been already shown that 52.5 per cent. of the energy contained in meat protein may be liberated in dextrose in the organism (see p. 132), and this may be directly used by the cells. The balance of the 71.4 per cent. of the directly available energy (= a residual 19 per cent.) is furnished by unknown compounds. As regards the source of the free heat nothing can be said with certainty. (See p. 361.)

CHAPTER VII.

THE INFLUENCE OF THE INGESTION OF FAT AND CARBOHYDRATES.

In a previous chapter it was shown that the amount of fat in the fasting organism materially affected the amount of protein burned. Where there was much fat present little protein was consumed; where there was little fat, much protein burned; and where there was no fat, protein alone yielded the energy necessary for life.

The ingestion of fat alone will not prevent the death of the organism because there is a continual loss of tissue protein from the body, which finally weakens some vital organ to such an extent that death takes place.

In a fasting animal which still contained fat, Voit[1] found that the ingestion of 100, 200, and 300 grams of fat scarcely influenced the protein metabolism. The latter was slightly increased, if anything. Voit's table is as follows:

Fat.	Urea.	Fat.	Urea.
0	11.9	300	12.0
0	12.0	0	11.9
100	12.0	0	11.3
200	12.4		

To another dog, which in starvation burned 96 grams of fat, 100 grams were given, with the result that he then burned 97 grams. The conditions of the metabolism in both cases were therefore identical. The fat ingested simply burned instead of the body's fat, but the total amount of protein and fat burned remained the same.

One reason why the ingestion of fat up to the requirement

[1] Voit: "Physiologie des Stoffwechsels und der Ernährung," 1881, p. 128.

does not alter the metabolism may be found in the observation of Schulz[1] that in starvation there is an increase in the quantity of fat in the blood, and of Rosenfeld[2] that the amount of fat in the liver increases. He finds that a fasting liver contains 10 per cent. of fat. If carbohydrates or protein (which yields carbohydrate in metabolism) be ingested, the fat content falls to 6.2 per cent. If fat be given to a fasting dog, the liver may contain 25 per cent. of fat; but if carbohydrates are ingested at the same time, the liver does not retain the fat, which must be deposited elsewhere. Thus, in the liver there is an antagonism between glycogen deposit, which follows carbohydrate ingestion, and fat deposition.

Pflüger[3] gave a dog fat alone in large quantities for thirty days and found that the fresh substance of the liver at the end of the period contained 45 per cent. of fat and no glycogen.

Miescher found fat globules in the muscle cells of salmon after their five to fifteen months' fast in fresh water, during which time they had laid their eggs. It is undoubted that the deposits of fat in the adipose tissue of these fishes are drawn on in starvation, and that the blood then carries to the hungry cells all the fat they require for their continued function. It seems that the fat supply to the cells is regulated by the quantity of other foods available, and that even in starvation there is at first ample fat to meet the requirement of the organism. These are important principles which will be further discussed when the subject of fatty infiltration is considered. (See chapter on Diabetes.)

As explained in Chapter VI, the small increase in metabolism after the ingestion of fat above the requirement has led Rubner[4] to determine accurately its specific dynamic action. The metabolism does not rise so greatly after the ingestion of

[1] Schulz: "Pflüger's Archiv," 1896, Bd. lxv, p. 299.
[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, Bd. ii, I, p. 86.
[3] Pflüger: "Pflüger's Archiv," 1907, Bd. cix, p. 123.
[4] Rubner: "Energiegesetze," 1902, p. 353.

fat as it does on a protein diet. If the hunger minimum of calories at 33° be 100, then 114.5 calories must be ingested in fat if a maintenance diet is to be given. This energy requirement is 140.2 in the case of protein diet. Protein therefore causes a much higher heat production than does fat. The influence of external temperature on the heat production after ingesting fat above the requirement is similar to that after meat ingestion, only not so pronounced. Rubner[1] gives the following table, showing the effect of the ingestion of 171.3 calories in fat per kilogram of dog:

SPECIFIC DYNAMIC ACTION OF FAT.

171.3 calories in fat per kg. dog were ingested.

	Calories per Kilo.		
Temperature.	Starvation.	After Fat Ingestion.	Increase.
2.7°	152.1	155.5	+ 2.2 per cent.
15.5°	83.1	93.4	+12.4 "
31.0°	64.5	79.9	+23.9 "

At 2.7° the excess ingested above the requirement amounted to 12.6 per cent., and the increase in heat production was 2.2 per cent.

At 31° the excess of food calories above the requirement was 165 per cent. and the increase in heat production was 23.9 per cent. In this instance 100 per cent. of the requirement may be calculated to raise the metabolism 14.4 per cent. at a temperature of 31°. This represents the specific dynamic effect of fat on the metabolism. As in the cases of the other foodstuffs, this action is to be explained by a production of heat in early cleavage processes which is not directly available for the cells of the organism.

It has already been demonstrated that less protein is burned in starvation when the body is fat than when it is lean. It would therefore seem that if protein and fat were ingested together, a similar reduction in the amount of the protein requirement would be effected (Voit).

[1] Rubner: "Energiegesetze," 1902, p. 119.

It has been shown in a previous chapter that nitrogenous equilibrium can be maintained in a dog only after the ingestion of three and a half times the quantity of protein destroyed in starvation. (See p. 109.)

E. Voit and Korkunoff,[1] continuing these experiments, find that if fat and meat be ingested together, the quantity of the latter necessary to establish nitrogenous equilibrium is reduced to between 1.6 to 2.1 times the starvation minimum. Much less protein food is therefore required to maintain the body's protein when it is ingested with fat than when it is given alone. In consequence of this, protein is more readily added to the body when fat is ingested with it, as is seen in the following experiment of Rubner[2] on a man.

INFLUENCE OF FAT INGESTION ON NITROGEN RETENTION.

Food.			N. Metabolism.	
N.	Fat.	Carbohydrates.	N in Excreta.	N to Body.
23.6	99.	260	26.36	—3.64
23.5	195.	226	21.55	+1.81
23.0	214.	221	18.5	+4.13
23.4	350.	234	17.6	+5.75

With increasing quantities of fat there is an increasing addition of protein to the body.

It has already been shown that protein ingested alone in large quantity establishes nitrogen equilibrium at a higher level, constantly raising the amount of heat produced until nitrogenous equilibrium is reached (the secondary dynamic rise, p. 151).

The same destruction of the easily oxidized protein takes place when it is given with fat, as was shown by Voit[3] in the following experiment on a dog:

[1] Voit and Korkunoff: "Zeitschrift für Biologie," 1895, Bd. xxxii, p. 117.

[2] Rubner: Von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 43.

[3] Voit: Hermann's Handbuch, "Physiologie des Stoffwechsels," 1881, p. 131.

THE "SECONDARY RISE" IN PROTEIN METABOLISM ON A MEAT-FAT DIET.

(Weights in grams.)

Food.			
Meat.	Fat.	Urea.	Flesh to Body.
1800	0	127.9	26
1800	0	127.6	26
1800	250	117.9	162
1800	250	113.5	171
1800	250	120.7	
1800	250	115.7	164
1800	250	119.7	
1800	250	127.5	11
1800	250	130.0	

A prolonged deposition of protein in the normal adult, even when fat is given with it, is demonstrably difficult.

The question arises, does the ingestion of large quantities of fat also cause an increase in the metabolism until fat combustion is balanced by its ingestion?

Rubner[1] has shown that this is not the case. He cites the record of the following long respiration experiment on a dog which was given 80 grams of meat and 30 grams of fat daily:

ABSENCE OF THE "SECONDARY DYNAMIC RISE" IN FAT METABOLISM ON A MEAT-FAT DIET.

(Fat being given in excess of the requirement.)

Calories of Metabolism.		
Protein.	Fat.	Total.
97.2	173.0	270.0
83.0	178.0	261.1
89.3	173.5	262.7
85.6	163.2	248.9
87.8	169.0	256.8
83.0	159.6	242.6
74.4	171.7	246.2
78.0	178.4	256.3
80.0	179.6	259.7

The diet was 58.7 per cent. above the starvation requirement. It contained 354 calories, of which 21.5 per cent. were in protein. The mean heat production during the period of ingestion of food was 256.0 calories, and in the following starvation days 223.2 calories, showing an increase in metabolism of 11.2 per cent. caused by an excess in food of 58.7 per cent. During

[1] Rubner: "Energiegesetze," 1902, p. 251.

the later days the animal was in nitrogenous equilibrium. Notwithstanding an excess of fat in the diet, and a continued deposit of fat in the body, there was no increase in the metabolism during the time of experimentation. The secondary dynamic action noted by Rubner as regards protein does not therefore take place as regards fat. The storage of fat in the body is consequently a matter of comparative ease.

Rubner[1] has compared the metabolism of a boy who was obese with that of his brother, who was a year older, but thin. They were the children of parents of small means and would not naturally be overfed. The interesting point of the experiment was whether obesity was due to a reduced metabolism with the consequent deposition of fat. Each boy was given a maintenance diet, or one which balanced his metabolism, without adding to or subtracting from his body substance. The general results are as follows:

	Fat Boy.	Thin Boy.
Age in years	10	11
Weight in kilograms	41	26
Total calories of metabolism	1786.1	1352.1
Calories per kilogram	43.6	52.0
Calories per sq. m. surface	1321.	1290.

The comparison shows that the fat brother had a larger total metabolism than the thin one, but the fat boy also had the larger surface. Per square meter of surface the metabolism was the same. The gradual increase in the area of the body caused by filling out the fat cells may therefore increase combustion, but this is not due to the specific action of the fat on metabolism as in the case of the secondary dynamic rise after protein ingestion, but rather to the increase in the size of the body. Carbohydrates, which in excess are converted into fat, must behave in the same way.

It will be noticed that in the experiment where 80 grams of meat and 30 grams of fat were daily ingested, although the protein metabolism gradually fell, the fat metabolism gradually

[1] Rubner: "Beiträge zur Ernährung im Knabenalter," 1902.

rose, and in isodynamic relation to the fall in protein. Allowing for the difference in specific dynamic action protein and fat replace each other in metabolism in isodynamic quantities.

Up to the present the discussion of metabolism has been confined to the combustion of protein and fat in starvation and after their ingestion. There is, however, another great class of foodstuffs which in man play a predominant part in nutrition,—the carbohydrates.

Starch, milk sugar, and cane sugar are all converted into monosaccharids in the intestinal tract, and dextrose, galactose, and levulose, formed from them, have similar physiological value in the cells. All three are glycogen formers, and thus galactose and levulose may be partly converted into dextrose through the glycogen stage.

It has already been noted that starvation greatly reduces the quantity of glycogen in the animal body. If under these circumstances dextrose, levulose, or galactose be ingested in considerable quantity and the animal be killed eight hours after the experiment, large quantities of glycogen are found stored in the liver and muscles. The amount in the liver may be as high as forty per cent. of the dry solids of that organ.[1] The quantity found is much more than could have originated from the protein metabolism of the time. There is therefore no doubt that these sugars are directly converted into glycogen through dehydration.

The quantity of glycogen present in a living animal cannot be accurately estimated. Schöndorf[2] gave seven dogs rich carbohydrate diets for several days and found that the quantity of glycogen present in their bodies varied between 7.59 and 37.87 grams per kilogram.

The distribution of this glycogen in 100 grams of the fresh tissue varied as follows:

[1] Voit: "Zeitschrift für Biologie," 1891, Bd. xxviii, p. 245.

[2] Schöndorf: "Pflüger's Archiv," 1903, Bd. xcix, p. 191.

	Maximum.	Minimum.
Liver	18.69	7.3
Muscle	3.72	0.72
Heart	1.32	0.104
Bone	1.90	0.197
Intestines	1.84	0.026
Skin	1.68	0.09
Brain	0.29	0.047
Blood	0.0066	0.0016

The traditional distribution of glycogen, one-half to the liver and one-half to the rest of the body, Schöndorf shows to be incorrect. For 100 grams of liver glycogen there occurred in the rest of the body the following amounts:

Dog I	398 grams.
" II	279 "
" III	87 "
" IV	76 "
" V	159 "
" VI	355 "
" VII	105 "

It is an interesting observation of Külz[1] and of Jensen[2] that an active organ like the heart maintains its normal glycogen content even after fifteen days of starvation.

In the various discussions on the subject of glycogen it has been shown that in starvation, and after protein and sugar ingestion, there is glycogen present in the body,—a constant supply always ready for emergencies, which can be reduced through exercise but which is only to be completely removed by tetanic convulsions (pp. 79 and 281).

The writer has here avoided the discussion of a production of sugar from fat. To his mind the evidence is against such production, as will be demonstrated in the chapter on Diabetes.

If carbohydrates be ingested alone immediately after starvation the protein metabolism may fall below the starvation amount. This appears in the experiments of Voit,[3] who gave a fasting dog 500 grams and noticed a fall in protein metabolism from 181 to 170 grams.

[1] Külz: "Festschrift zu Ludwig," 1891, p. 109.

[2] Jensen: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv, p. 525.

[3] Voit: Hermann's Handbuch, "Stoffwechsel," 1881, p. 140.

Rubner[1] was able to reduce the nitrogen in the urine of a man from 11.9 to 6.3 grams, or nearly one-half, by causing the subject to ingest a diet rich in carbohydrates.

This higher protein-sparing property gives to dogs fed on carbohydrates alone a longer lease of life than is granted to those fed on fat alone, although the ultimate outcome is the same.

The effect of feeding with easily absorbable sugar in excess is shown in the following experiment of Rubner[2] on a dog:

INFLUENCE OF CANE SUGAR ON THE METABOLISM OF A DOG.

Food.	N in Excreta in Grams.	C Retained from Carbohydrates in Grams.	Cal. from Protein.	Cal. from Fat or Carbohydrates.	Calories, Total.
Starvation	1.92	....	48.0	203.4	251.4
Starvation	1.82	....	45.5	208.0	253.0
85 grams cane sugar	0.91	10.18	22.7	224.4	247.1
110 " " "	0.72	17.81	18.0	245.9	263.9
110 " " "	0.56	17.61	14.0	247.7	261.7
120 " " "	0.53	6.70	13.2	....	....
Starvation	0.69	....	17.2	208.8	226.0

The protein metabolism may thus be reduced to one-third the fasting value, a result also obtained by Landergren[3] and by Folin[4] in man. Cathcart[5] gave a man who had been fasting fourteen days a diet of cream (300 c.c.) and starch (400 grams). The nitrogen excretion in the urine was as follows:

	Total N.	Urea N.
Day 14 of starvation	7.78	5.99
" 1 on cream-starch diet	7.43	5.80
" 2 " " " "	3.58	2.29
" 3 " " " "	2.84	1.76

The absence of a fall in protein metabolism on the first day is probably to be explained by assuming a large deposit of glycogen

[1] Rubner: von Leyden's Handbuch, 1903, vol. i, p. 44.

[2] Rubner: "Die Gesetze des Energieverbrauchs," 1902, p. 341.

[3] Landergren: "Skan. Archiv für Physiologie," 1903, Bd. xiv, p. 112.

[4] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 45.

[5] Cathcart: "Biochemische Zeitschrift," 1907, Bd. vi, p. 109.

within the body at the expense of the starch ingested (see p. 147). On the third day of the diet the protein metabolism had fallen to one-third that observed in fasting.

The quantity of sugar utilized by Rubner's dog above mentioned was 35.7 to 80.6 per cent. above the starvation requirement for energy (the cane sugar eliminated in the urine was deducted from that ingested, in order to determine the quantity utilized). The experiment was done at 33°, and the specific dynamic action of the cane sugar may be calculated as raising the metabolism 5.36 per cent. on an average.

The experiment also illustrates the ready retention of carbohydrate carbon in the body. It is well known that such carbon may be stored in the body as glycogen, but its retention often exceeds the animal's ability to hold glycogen.

Voit, when he wrote his "Physiologie des gesammt Stoffwechsels und der Ernährung," in 1881, was unable to give definite proofs of the conversion of carbohydrate into fat in the organism, although such conversion was popularly believed to take place.

Definite proof of the conversion of carbohydrates into fat was afforded by Meissl and Strohmer,[1] who gave a pig, weighing 140 kilos, two kilograms of rice containing 1592 grams of starch daily for seven days, and collected the carbon and nitrogen of the excreta by means of a Pettenkofer-Voit apparatus during two days of the period. The average results per day were as follows:

	Carbon.	Nitrogen.
Ingested in food	765.37	18.67
Excreted	476.15	12.59
Balance retained in the body	289.22	6.08

The nitrogen retained represented 38 grams of protein containing 20.1 grams of carbon; 269.12 grams of retained carbon were therefore available for glycogen or fat construction. Since the amount of carbon retained exceeded the possible glycogen

[1] Meissl and Strohmer: "Sitzungsberichte der k. Acad. d. Wissenschaften," 1883, Bd. lxxxviii, III Abtheilung.

formation, fat must therefore have been added to the body. Had all the carbon retained been converted into fat it would represent a production of 343.9 grams of fat. Of this only 33.6 grams of fat could have arisen from the protein metabolism of the period. Hence it is possible that 310.3 grams of fat may have originated from 1592 grams of starch ingested, which indicates a conversion of 19.5 per cent. of the starch given into fat.

Similar experiments were made with geese by E. Voit and C. Lehmann.[1] The geese were starved four and a half days and were then fed with rice.

One of these respiration experiments which lasted thirteen days has recently been published[2] and is as follows:

	Nitrogen.	Carbon.
In the 2609 grams of rice	41.47	1159.7
In the excreta—		
Urine and feces	45.39	134.8
Respiration	....	657.8
Total	45.39	792.4
Change in the body	—3.92	+367.3

At the commencement of the experiment the animal weighed 4 kilograms. There was no protein retention, but 31 per cent. of the carbon ingested was not eliminated. The protein metabolism could not nearly yield enough carbon to account for that retained. As the rice contained but 0.51 per cent. of ether extract the retained carbon could not have been administered in the form of fat. If 367.3 grams of carbon had been retained in the form of glycogen this would have aggregated 851 grams, or twenty per cent. of the whole goose. This is a manifest impossibility, since E. Voit[3] found only 2.2 per cent. of glycogen in a goose which had been largely fed on rice. Since the carbon retained could not have been stored as glycogen, the only alternative remaining is to assume its retention as fat.

Rubner at the same time showed the same principles to be true in the case of the dog.

[1] Voit: "Sitzungsberichte der kgl. bayr. Acad. d. Wissenschaft," 1885, p. 288.

[2] Lehmann and E. Voit: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 644.

[3] E. Voit: "Zeitschrift für Biologie," 1888, Bd. xxv, p. 543.

It is evident, then, that pigs, geese, and dogs can convert carbohydrates into fat. The fattening of cattle may be similarly accomplished.

The ability to convert carbohydrate into fat probably exists throughout the animal kingdom. Thus Weinland[1] has expressed from living ascaris ferments which convert glycogen into dextrose and then into valerianic and possibly caproic acids,—0.8 gram of dextrose yields 0.3 gram of valerianic acid. (See p. 310.)

This is suggestive of a wide-spread biological capability.

When carbohydrates are converted into fat in the organism the respiratory quotient ($\frac{\text{Volume } CO_2}{\text{Volume } O_2}$, see p. 28) may rise very considerably above unity. This is for the reason that an oxygen rich substance like dextrose is being converted into substance which is poor in oxygen. This intramolecular oxygen derived from dextrose becomes available for carbon dioxid production and the requirement for inspired oxygen diminishes. Hence the volume of expired carbon dioxid may be greater than the volume of inspired oxygen. Max Bleibtreu[2] found that the respiratory quotient of a goose which had been stuffed with grain was 1.33, whereas the same goose when fasting showed a normal quotient for that condition of 0.728. Pembrey[3] describes how marmots previous to the winter hibernation instinctively devour large quantities of carbohydrate food, and how the respiratory quotient may rise even as high as 1.39. This indicates a fat production for use during the winter.

Johansson, Billström, and Heijl[4] have shown that if 50 to 200 grams of cane sugar be given a fasting man, the carbon dioxid output increases from 22.6 grams per hour to about 30 grams per hour. The larger ingestion does not produce a higher elimination of carbon dioxid than does the smaller amount.

[1] Weinland: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 55; Bd. xliii, p. 86; 1903, Bd. xlv, p. 113.

[2] Bleibtreu: "Pflüger's Archiv," 1901, Bd. lxxxv, p. 345.

[3] Pembrey: "Journal of Physiology," 1901, vol. xxvii, p. 407.

[4] Johansson, Billström, and Heijl: "Skan. Archiv für Physiologie," 1904, Bd. xvi, p. 263.

This indicates the evenness with which sugar entering the blood-stream is utilized by the organism. If sugar be present in excess it may be stored as glycogen until it is needed by the cells. The increased carbon dioxid output does not mean increased metabolism in the sense of increased heat production, but the increase due to the destruction of carbohydrates instead of fat in the production of the same amount of heat. The rise in the carbon dioxid output is greater after levulose is ingested than after dextrose is given. This is explained as due to the fact that levulose is less readily retained in the liver as glycogen and therefore reaches the tissues in a larger stream than does dextrose under similar circumstances, and hence more completely replaces fat as the source of energy. In a later paper Johansson[1] explains that after ingesting 200 grams of dextrose containing 740 calories, or one-quarter the man's energy requirement for a day, the rise in carbon dioxid output lasts for six hours and then falls to the fasting basis. This is an indication of the ready absorption and combustion of ingested dextrose. If there has been prolonged fasting ingested dextrose may cause no rise in the carbon dioxid output in man on account of its conversion into glycogen. (See p. 147.)

The truth of the statement that carbohydrates exactly replace an isodynamic equivalent of fat is illustrated by Rubner's[2] experiment on a man in which he compared the production of energy in starvation with that produced after the ingestion of one and one-fifth that requirement in the form of cane sugar. For the sake of emphasis the metabolism after giving one and one-fifth the starvation requirement in the form of meat is also printed:

Starvation	2042 calories.
Sugar (120 per cent. of requirement)	2087 calories.
Meat (120 per cent. of requirement)	2566 calories.

It has been seen that carbohydrates ingested alone diminish the protein metabolism. This reduces the specific dynamic

[1] Johansson: "Skandin. Archiv für Physiologie," 1908, Bd. xxi, p. 30.

[2] Rubner: "Energiegesetze," 1902, p. 410.

action of protein in the general metabolism and the small specific dynamic action of sugar scarcely changes the total metabolism from the starvation requirement.

Any excess of sugar above the requirement for energy is retained in the body either in the form of glycogen or as fat.

The contrast given above between the results of the ingestion of carbohydrates and of meat is extremely striking.

It is evident that the carbohydrate food protects protein tissue from waste better than do other foodstuffs, and as a source of energy is the most economical.

When carbohydrates and protein are ingested together in quantity sufficient for the requirement of the organism, it has been found that, taking the starvation protein metabolism as one, nitrogen equilibrium can be maintained by ingesting one part of protein.[1]

The work of Siven,[2] however, was the first indication that nitrogen equilibrium may be maintained at even a lower level than that ordinarily present in starvation. A somewhat undersized healthy man weighing 60 kilograms, who normally ate a mixed diet containing 16 grams of nitrogen, was given less and less protein and an attempt was made to establish nitrogen equilibrium at lower and lower levels. The daily ration was rich in carbohydrates and yielded 2444 calories. This must have been considerably in excess of the requirement.

The experiment was divided into four periods of about a week each, which may be summarized as follows:

Length in Days.	N in the Food.	Days until N Equilibrium was Obtained.	N loss before N Equilibrium was Obtained.	Total N to Body.
I, 7	12.69	1	0.53	+9.73
II, 8	10.40	1	0.34	+6.04
III, 6	8.71	at once	. . .	+4.39
IV, 6	6.26	3	2.09	—0.58

[1] E. Voit and Korkunoff: "Zeitschrift für Biologie," 1895, Bd. xxxii, p. 117.

[2] Siven: "Skan. Archiv für Physiologie," 1900, Bd. x, p. 91.

It is apparent that nitrogen equilibrium may be established after ingesting 6.26 grams of nitrogen, although, as has been seen, the elimination during the early days of starvation in man is usually 10 grams. During the first three periods of reduced protein intake, as much as 20.16 grams of protein nitrogen were actually added to the body. In a fifth period nitrogen equilibrium was obtained on the fourth day on a diet containing 4.52 grams of nitrogen.

The susceptibility of the protein metabolism to sudden withdrawal of carbohydrates was shown by Lusk[1] upon himself. Nitrogen equilibrium was nearly established in two different experiments at different levels, with the ingestion of 20.55 and 9.23 grams of nitrogen respectively. In the first experiment withdrawal of 350 grams of carbohydrates from the mixed diet caused a rise in nitrogen metabolism from 19.84 to 27.00 grams, incurring a loss of body nitrogen of 6.45 grams. In the second experiment withdrawal of the carbohydrates increased the nitrogen excretion from 11.44 to 17.18, a loss to the body of 7.95 grams. The losses are for the second day after the withdrawal of the carbohydrates, since the metabolism remains under the influence of the glycogen supply during the first day.

Subsequent experimentation has shown that *partial* replacement of carbohydrates by fat in the diet may have no influence, or only a transitory one, upon the amount of protein metabolized. This is of value in practical dietetics. Tallquist[2] established nitrogen equilibrium in a man with a diet containing about 16 grams of nitrogen, 10 per cent. of the calorific value being contained in protein and 90 per cent. in carbohydrates. On replacing one-third of the carbohydrate calories in the diet with fat calories an increased protein metabolism was observed for two days, followed by nitrogen equilibrium on the third day. The food given contained 35 calories per kilogram, a moderate quantity, and was made up as follows:

Period I. 16.27 g. N + 44.6 g. Fat + 466 g. Carb. = 2866 Cal.
" II. 16.08 g. N + 140.1 g. Fat + 250 g. Carb. = 2873 Cal.

[1] Lusk: "Zeitschrift für Biologie," 1890, Bd. xxvii, p. 459.
[2] Tallquist: "Archiv für Hygiene," 1902, Bd. xli, p. 177.

The nitrogen elimination was as follows:

	Day.	N Excreted.	N Balance.
Period I.—	1	17.11	—0.84
	2	14.40	+1.86
	3	14.65	+1.62
	4	15.58	+0.69
" II.—	5	17.66	—1.58
	6	17.32	—1.24
	7	15.94	+0.14
	8	16.22	—0.14

This proves that with a diet containing 16 grams of nitrogen in protein, nitrogen equilibrium is about as easily maintained on a mixed diet, including carbohydrates and fats, as when only carbohydrates are allowed with the protein.

Incidentally it may be remarked that in diseases of the liver, such as catarrhal jaundice, hepatic cirrhosis, cholelithiasis with jaundice and in cases of engorgement of the liver more carbohydrates are needed to maintain nitrogen equilibrium than normally is the case.[1] Tallquist warns against thinking that the tendency towards a higher protein metabolism here manifested is due to toxic influences, but believes that the cause lies in the fact that glycogen can no longer be effectively stored in the liver.

The sparing influence of carbohydrate oxidation upon protein metabolism has been beautifully illustrated by Landergren.[2] Diets containing carbohydrates and fats, but scarcely any nitrogen (about one gram daily), were given men and the protein metabolism noted. This condition is called that of *specific nitrogen hunger*. After four days' administration of such a diet the urinary nitrogen may be reduced to less than four grams.

In one experiment in which this was accomplished carbohydrates were entirely replaced by fat with the result that protein metabolism rose to the amount found in starvation (about 10 grams). It has already been explained that ingestion of fat alone will not affect protein metabolism in starvation. The experiment is as follows:

[1] Tallquist: "Archiv für Hygiene," 1908, Bd. lxv, p. 39.

[2] Landergren: "Skan. Archiv für Physiologie," 1903, Bd. xiv, p. 112.

Carbohydrate Period. Diet = 45.2 Cal. per Kg. N in Urine.		Fat Period. Diet = 43.7 Cal. per Kg. N in Urine.	
Day 0	*12.76	Day 5	4.28
" 1	....	" 6	8.86
" 2	....	" 7	9.64
" 3	....		
" 4	3.76		

* Ordinary diet.

On day 5, the first of the fat diet, it is evident that the protein metabolism was affected by the use of the glycogen supply of the body, an influence which became negligible on the second and third days of the fat diet (p. 56).

Landergren gives the following results in various cases of specific nitrogen hunger, showing the nitrogen in the urine before the diet, and after four days thereof:

	II.	III.	IV.	V.
N in urine (ordinary diet)	12.76	11.87	13.7	15.2
N in urine (specific N hunger)	3.76	3.95	3.04	4.2
Calories in diet per kg	45.2	37.8	45.0	38.4

This reduction of protein metabolism to four grams on the fourth day was brought about by the following diets in the different cases:

II. 750 g. carbohydrates = 45.2 cal. per kg.
III. 300 g. carbohydrates + 150 g. fat = 37.8 " " "
V. 380 g. carbohydrates + 150 " " = 38.4 " " "

A diet containing half its calories in carbohydrates and half in fat has therefore the same protein protecting power as one made up of carbohydrates alone. This demonstrates the rationality of a mixture of the non-nitrogenous foodstuffs.

Landergren finds that on a diet containing two-thirds of the calorific requirement the urinary nitrogen on the fourth day may be eight grams, or nearly the fasting quantity. The diet was made up of—

X. 240 g. carbohydrate + 64 g. fat = 21.8 cal. per kg.

Therefore, in specific nitrogen hunger with undernutrition, the nitrogen eliminated in the urine appears to be increased. It is a pity that this statement rests on only one experiment, for it does not appear in accord with the following work of Chittenden.

Chittenden[1] finds that nitrogen equilibrium may be maintained on a diet containing a very small amount of protein and two-thirds of the body's requirement of energy. The first experiment was on Fletcher and lasted six days. The daily ration contained 7.19 g. nitrogen + 38.0 g. fat + 253 g. carbohydrates = 21.3 calories per kg. The excreta contained 6.90 grams of nitrogen daily. On this diet the individual showed "remarkable physical strength and endurance."

Another experiment was performed by Chittenden on himself and lends itself for interesting comparison with the results of the ingestion of a maintenance ration. The food was principally vegetable. The results may be thus tabulated:

A LOW LEVEL OF NITROGEN EQUILIBRIUM IN NORMAL AND UNDERNUTRITION.

Date.	Diet.		N Excretion.	N Balance.
	N in Grams.	Cal. per Kg.		
March 23.....	6.79	34.7	6.56	+0.23
March 25.....	6.88	22.4	6.34	+0.54

Nitrogen equilibrium may therefore be maintained at a low level even during the state of undernutrition present when 22.4 calories per kilogram are in the daily diet. On a milk diet Rubner[2] found that the ingestion of 2483 grams of milk containing 84 grams of protein and two-thirds the body's requirement of energy resulted in the addition of 6.7 grams of protein to the body daily for three days (p. 224).

It is a valuable piece of information to know that one may diet an obese patient on a food containing little protein and two-thirds the body's energy requirement without danger of protein loss. The other third of the necessary energy will be furnished by the body's own store of fat. It is not remarkable that

[1] Chittenden: "Physiological Economy in Nutrition," 1904, pp. 14, 40.

[2] Rubner: "Zeitschrift für Biologie," Bd. xv, 1879, p. 130.

the body is capable of great physical effort on such a diet, for a fasting man is also competent in this direction (p. 80).

In the last chapter mention was made of the sparing action of gelatin on protein metabolism, and its ingestion was found to prevent about 23 to 37.5 per cent. of the protein loss during starvation. Murlin[1] in an extensive series of experiments has shown that the sparing power of gelatin is greater than this when it is ingested with a mixed diet. He finds that if the quantity of nitrogen eliminated in fasting be taken as one, then nitrogen equilibrium may be maintained in dogs and in man on ingestion of a diet rich in carbohydrates whether the nitrogen of the diet be protein nitrogen equal to one, or whether it contain one-third protein plus two-thirds gelatin nitrogen. This is shown in the following experiment on a man, the results being expressed in averages per day.

EFFECT OF SUBSTITUTING GELATIN FOR PROTEIN IN A MIXED DIET IN MAN.

N elimination on a third day of fasting = 13.23 g.

Source of N in Diet.	No. of Days.	Calories in Food.	Cal. per Kg.	N in Food (Grams).	N in Excreta (Grams).	N to Body (Grams).
All protein N.....	3	3208	47	14.25	13.33	+0.87
Two-thirds (63%) gelatin N + one-third protein N	2	3620	51	14.53	13.82	+0.71
All protein N.....	2	3220	46	14.26	13.52	+0.74

Murlin[2] also showed that the sparing power of gelatin was due to its immediate chemical nature and not to the sixty per cent. of dextrose which can arise from it in metabolism. (See p. 132.) For example a fasting dog was given 12 grams of dextrose daily for four days after thirteen days of fasting; then 20 grams of gelatin were substituted during a period of four days. The dextrose scarcely exerted any sparing power over

[1] Murlin: "American Journal of Physiology," 1907, vol. xix, p. 285.
[2] Murlin: "American Journal of Physiology," 1907, vol. xx, p. 234.

the protein metabolism, whereas the ingestion of gelatin showed the usual sparing of 31 per cent.

The same fact was demonstrated on a man who was brought into nitrogen equilibrium on an adequate mixed diet containing 10 grams of nitrogen and carbohydrates enough to supply fifty per cent. of the energy. The state of nitrogen equilibrium was not quite maintained on substituting gelatin for two-thirds of the protein nitrogen in the diet. Murlin explained this as being due to a dislike for sweets on the part of the individual so that he could not take carbohydrates in large excess. However, when the nitrogen of the diet was reduced so as to contain only protein nitrogen equal to one-third that eliminated in fasting, together with the sixty per cent. of dextrose which could have originated from the gelatin previously ingested, the waste of body nitrogen rose far above that observed when gelatin and protein were given. The experiment may thus be presented.

INFLUENCE OF GELATIN IN METABOLISM.

Figures are for the last day of each period.

Source of N in Diet.	No. of Days.	Calories in Food.	Cal. per Kg.	N in Food.	N in Excreta.	N to Body.
All protein N.....	4	1971	43	10.05	10.35	—0.30
Two-thirds (67%) gelatin N + one third protein N	6	1935	42	9.62	10.12	—0.50
One-third protein N.....	3	1858	40	3.23	5.62	—2.39

Here the rise in the metabolism of body protein corresponds to the withdrawal of gelatin from the diet even in the presence of a considerable intake of carbohydrate. Hence Landergren's[1] interpretation that the rise in nitrogen elimination which takes place on changing from a pure carbohydrate to a pure fat diet, is due to the body's absolute requirement for carbohydrate and that it obtains this by increasing its protein metabolism is scarcely tenable.

[1] Landergren: Inaugural Dissertation, 1902: "Maly's Jahresbericht," 1902, p. 685.

The true explanation of these experiments will be apparent after a discussion of Rubner's work concerning the "wear and tear" quota, which follows at the end of the chapter. (See p. 186.) It will then be evident that the "wear and tear" quota of protein metabolism must be covered by the ingestion of an equal amount of "repair" quota, while the additional "dynamic" quota may be supplied by protein or by gelatin. Murlin found that the "repair" quota was best administered in the form of beef heart, and that the proteins of biscuit meal were very inefficient as sparers of body protein.

In the course of his experiments Murlin found that the longer the animal had fasted, that is, the lower its protein condition, the more readily did gelatin reduce the waste of body protein.

Murlin also showed that three-quarters of the starvation nitrogen ingested as gelatin and one-quarter as protein were not able to maintain nitrogen equilibrium in the dog. Two-thirds the starvation nitrogen requirement ingested as gelatin and one-third as protein maintain nitrogenous equilibrium. Carbohydrates ingested alone reduce protein metabolism to one-third that found in starvation. One-third the starvation quantity seems to be the limit of protein metabolism compatible with life.

It may also be noted that in a fasting diabetic dog the protein metabolism may rise to five fold that noted in simple fasting (see p. 285) or fifteen fold the *irreducible minimum* of the "wear and tear" quota. Under these circumstances the writer has found that pure gelatin given alone is more effective as a protein sparer than it is in simple fasting. Thus after giving 30 grams of gelatin to a fasting phlorhizinized dog the following results were obtained on analyzing the urine every twelve hours:

	Dextrose.	N.	Body N.
Fasting, 12 hours	12.58	3.77	—3.77
Gelatin (= 4.644 g. N) 12 hours	20.66	6.02	—1.37
Fasting, 12 hours		3.79	—3.79

If the fecal nitrogen, which is very small after gelatin ingestion, be neglected, it may be calculated that body protein

was spared to the extent of 63.7 per cent. after the administration of gelatin, instead of 30 per cent. as in ordinary fasting. One may therefore conclude that the great waste of body protein which takes place in diabetes belongs in Rubner's category of "dynamic" protein metabolism, for which gelatin may be largely used as a substitute.

Since carbohydrates so effectively spare protein from combustion it would seem logical that their use should render the retention of protein in the body easier than when fat is given with protein.

Lüthje[1] finds a long continued nitrogen retention in man when much nitrogen in protein is ingested (up to 50 g. N daily!) and carbohydrates and fat making a total of 4000 calories or 66 calories per kilo. (See also Bornstein's experiment, p. 110.)

In a subsequent paper Lüthje[2] finds that the P_2O_5 retention in convalescence is that which corresponds to the retention of protein for the formation of new tissue including bone. Sometimes in a healthy person not enough P_2O_5 is retained to build up "flesh," and the protein retained must therefore exist in the form of "deposit protein." This protein, he says, is not stored in the blood, for the composition of the blood does not alter; but is perhaps retained in the cellular fluids, just as glycogen is retained by the cells.

Rubner[3] has lately given attention to the protein requirement of the cells. Reference has already been made (p. 74) to the "wear and tear" quota represented by the protein metabolism of a dog maintained on a diet of pure fat in quantity sufficient to cover the requirement for energy. This quota is reduced when carbohydrates are ingested so that it may amount to only four per cent. of the total energy requirement. The following statements hold true if an animal be given the maintenance

[1] Lüthje: "Zeitschrift für klinische Medizin," 1902, Bd. xliv, p. 22.

[2] Lüthje: "Deutsches Archiv für klinische Medizin," 1904, Bd. lxxxi, p. 278.

[3] Rubner: "Archiv für Hygiene," 1908, Bd. lxvi, p. 45.

requirement of energy in the form of non-nitrogenous foodstuffs. Otherwise if protein be ingested it will itself be used to supply the energy requirement (compare with work of Schulz, p. 76). The "wear and tear" quota must be covered by the ingestion of a "repair quota." Ingestion of protein beyond the amount needed for the repair of the normal waste may first be used for growth. The portion used for growth is called the "growth" quota and is dependent on the protein condition of the cells. The conditions which determine the "wear and tear" metabolism and those which determine growth are entirely dissimilar, although without metabolism growth is impossible. If protein be administered beyond the requirement of the cells for repair and for growth, then the excess constitutes a "dynamic" quota which after deamination serves to furnish energy to the cells in the same fashion as do fat and sugar.

Rubner states that the greater the impoverishment of the protein supply in an animal fed with fat, the more powerful is the protective effect of small quantities of ingested protein over the loss of body protein. Also the retention of protein depends on the protein content of the animal as well as on the quantity of protein ingested. This is illustrated in the following table.

INFLUENCE OF THE PROTEIN CONTENT OF A DOG ON THE RETENTION OF PROTEIN INGESTED.

Total N Content of Dog.	N in Terms of 100 N in Dog in Food.	to Body.
318.8	5.25	+1.65
354.7	5.57	+1.02
310.6	6.72	+2.64
363.7	12.79	+2.62

It is evident from this, that of the same diet of protein more will be retained when the nitrogen content of the dog is low than when it is high; and also that a small protein intake may cause the same retention of nitrogen as a large protein intake, if in the first instance there be a relative impoverishment of the protein content of the animal.

According to these laws adult cells which have been depleted

of their protein may gradually improve their nutritive condition until they reach an *optimum*, at which point they lose their power to attach additional protein.

The question arises, To what extent may the amino-bodies formed within the intestine be regenerated into protein? It is believed that the cells of the intestinal villus regenerate fat from fatty acid and glycerin, since neutral fat alone is found in the thoracic duct. But all the starch fed is not regenerated into starch, nor is maltose regenerated into maltose in the body. Much may be burned as dextrose and only a part is transformed into glycogen. Long ago Schultzen and Nencki[1] stated that a certain portion of the amino-bodies formed in digestive proteolysis was absorbed and oxidized, and that the absorbed protein itself followed the lines of an enzymotic cleavage into amino-bodies. In the light of newer knowledge several authorities have recently elaborated theories along similar lines. It has been pointed out by Folin[2] that there is little evidence of reconstruction of all the protein ingested. He cites the experiments of Nencki and Zaleski,[3] which showed that the portal blood during digestion contains four times as much ammonia as arterial blood, and that the mucosa of both stomach and intestine yields large quantities of ammonia. The inference is that the ammonia of the portal vein is derived from ammonia produced in the mucosa as well as from that which normally originates in the intestine during tryptic proteolysis.

Modern theory suggests the deamination of the larger part of the amino-acids formed in intestinal digestion within the intestinal wall itself. It is possible that the "dynamic" quota of Rubner is always so treated instead of being first converted into serum proteins in accordance with Abderhalden's ideas. The "repair" quota and the "growth"

[1] Schultzen and Nencki: "Zeitschrift für Biologie," 1872, Bd. viii, p. 124.

[2] Folin: "American Journal of Physiology," 1905, vol. xiii, p. 117.

[3] Nencki and Zaleski: "Zeitschrift für physiologische Chemie," 1901, Bd. xxxiii, p. 206.

quota must, however, be furnished either in the form of blood proteins or of amino-acids which have passed the intestines. It is well known that the nutritive condition of the cells determines the passage of fat from the fat repositories in the body, and it may be questioned whether the nutritive condition of the cells may not determine either the passage of amino-acids through the intestinal wall (or their synthesis within it), instead of their deamination there. If at times the amino-acids pass through the intestinal wall into the blood stream, as the work on "amino-sugars" (pp. 123 and 124) renders probable, then their synthesis to new protein might be accomplished in the liver, in muscle or possibly in all tissue.

The conditions of protein metabolism are entirely similar to those of starch metabolism: (1) digestive hydrolysis; (2) partial combustion of the end-products; and (3) possible regeneration of portions of the end products into substances akin to the originals but characteristic of the organism,—*i. e.*, glycogen and body proteins. In the case of proteins the second or metabolic process involves the production of sugar and of fatty acids from the amino-acids involved. The third or regenerative process is promoted by such a protein as casein, which yields a large variety of cleavage products.

In conclusion, it may be said that carbohydrates are the most economical of the foodstuffs, both physiologically and financially. They are the greatest sparers of protein. Ingestion of fat has for its object the relieving of the intestine from excessive carbohydrate digestion and absorption. Ingestion of fat in too large quantities leads to digestive disturbances, and if carbohydrates are entirely abandoned, to acetonuria.

CHAPTER VIII.

THE INFLUENCE OF MECHANICAL WORK ON METABOLISM.

In the account of metabolism during starvation, a short description has already been given of the influence of mechanical work on protein metabolism, of the influence of posture on general metabolism, and of the relation of the amount of metabolism to the diurnal variations of human temperature.

The source of mechanical work must be from metabolism, for mechanical energy cannot be derived from nothing. The necessary energy might be obtained in one of two ways, either at the expense of a proportionate reduction in the quantity of heat liberated by the resting organism, or by an increase in the amount of the metabolism. In the former case work would diminish the heat production, and might cool the tissues, which is not observed to take place. If work were done at the expense of increased metabolism, and if this increase were completely converted into mechanical effect, then the heat production in the organism might remain the same as in the resting state. If, however, the result of mechanical effort be a stimulation of metabolism to the extent of not only enabling the body to do work, but also causing it to produce more heat than when at rest, then the tendency of the tissues must be to grow warmer, perhaps with a resulting outbreak of sweat to reduce the body temperature through physical regulation. The last named is the actual process.

Lavoisier's discovery that the absorption of oxygen is increased during mechanical exercise, firmly established the fact of a higher metabolism under these conditions.

The first experiments in which the effect of work upon the

total metabolism was demonstrated were made upon a man by Pettenkofer and Voit.[1] A man turned an ergostatic wheel 7500 revolutions on each working day for a period of nine hours, which afforded sufficient exercise to cause great fatigue at the end of the day. The experiments were made both during hunger and when the man was ingesting a medium mixed diet. The food supplied in the mixed diet contained:

	Grams.	Calories.
Protein	121.7	506
Fat	117.	1088
Carbohydrates	352.	1443
Total		3037

The metabolism of this man, a strong workman, weighing seventy kilograms, at rest and at work, starving or on the medium mixed diet as given above, is presented in the following table:[2]

EFFECT OF MECHANICAL WORK ON METABOLISM IN MAN.

	Grams Metabolized.			Cal. of Metabolism.	Cal. above Fasting Quantity.	Experiment No. of Pettenkofer and Voit.
	Protein.	Fat.	Carbohydrates.			
Starvation—Rest ...	70.8	222		2374		I
" —Rest ...	68.7	208		2231		III
" —Work ..	66.1	387		3882	1582	IV
Mixed Diet—Rest ..	121.7	73	352	2638	336	V
" —Rest ..	118.7	93	352	2714	412	VI
" —Rest ..	125.0	84	352	2750	458	VII
" —Work .	121.7	208	352	3856	1554	VIII
" —Work .	122.0	152	352	3378	1076	IX

From these early experiments it was evident that mechanical work did not increase protein metabolism even in starvation,

[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1866, Bd. ii, p. 537.

[2] I have multiplied the nitrogen of the ingesta and excreta by 6.25 to obtain the quantity of the protein given and metabolized. The ratio N : C = 1 : 3.28 in protein has been employed. The dry starch has been calculated as containing 44.2 per cent. and the fat as containing 76.5 per cent. of carbon, which were the figures used by Pettenkofer and Voit. Rubner's standard calorimetric values have been used. (See Introductory Chapter.)

but that the power to do work might readily be supplied by the increased metabolism of fat.

It is interesting to note the increase of the metabolism above the fasting minimum in the above circumstances. This relation is embodied in the following table:

	Calories of Metabolism.	Increase.
Starvation—Rest (average)	2302	
" —Work	3882	1582
Medium diet—Rest (average)	2717	415
" —Work	3856	1554
" —Work	3378	1076

This table indicates a specific dynamic action of the food amounting to 415 calories. Another conclusion may be drawn from the table, and one which, if true, is of importance; it is that *during the working days the specific dynamic action of the food does not appear.* In other words the metabolism during work on a mixed diet is not greater than during starvation when the same amount of work is being effected. It may be that the free heat liberated as the result of the specific dynamic action of the food can be utilized in warming the cells in the service of the production of mechanical energy, just as it is used in lieu of the heat produced through chemical regulation. If this be true, giving protein to men at work—for example, athletes—would not entail economic waste of the fraction usually lost when it is given during rest.

Rubner[1] shows that a man of seventy kilograms weight, developing mechanical energy to the extent of 15,000 kilogram-meters per hour, produces practically the same quantity of carbon dioxid, no matter what the temperature of his environment may be. The results of the experiment are as follows:

Temperature of the Air.	Percentage Moisture in the Air.	Carbon Dioxid per Hour in Grams.	Water Excreted per Hour in Grams.
7.4°	81	84.0	58.0
12.7°	84	78.5	70.8
16.7°	59	97.0	138.1
17.5°	87	84.5	90.4
18.8°	83	81.2	112.8
25.0°	47	78.7	230.0

[1] Rubner: Von Leyden's Handbuch, "Die Ernährungstherapie," 1903 Bd. i, p. 74.

This person while at rest and at a temperature of 21.1° excreted 33.6 grams of carbon dioxid and 42 grams of water.

It is clear that during work the metabolism is independent of surrounding temperature, of climatic conditions. In other words, *during mechanical work the influence of the "chemical regulation" of body temperature may be eliminated.* (See p. 92.) The extra heat production in doing mechanical work is utilized instead of the production of heat which is excited reflexly through cold. These results were forecast by Voit.[1]

Generally speaking, neither clothing nor temperature affects the amount of the metabolism during exercise. They influence only the quantity of water eliminated in the perspiration, in the effort of the body to maintain its normal temperature through physical regulation. It is evident from Rubner's details of the water excretion that at a low temperature the extra heat production during mechanical exercise is lost by radiation and conduction. Rubner explains that the slight increase in the excretion of water above that lost while at rest, is due to its increased evaporation through increased respiratory activity. At a higher temperature conduction and radiation become insufficient to cool the body, and a large proportion of the loss of heat takes place at the expense of the evaporation of sweat.

In hot, moist climates, however, the cooling of the body through the evaporation of moisture becomes difficult, and this is especially pronounced in the case of fat people (p. 103), who with difficulty discharge the heat produced within them. Broden and Wolpert[2] show the effect of the action of temperature and humidity on the metabolism of a fat man, weighing 101 kilograms, who executed the same amount of mechanical work under various conditions of experimentation. The work was light, being 5375 kilogrammeters per hour. The results were as follows:

[1] Voit: "Zeitschrift für Biologie," 1878, Bd. xiv, p. 152.

[2] Broden and Wolpert: "Archiv für Hygiene," 1901, Bd. xxxix, p. 298.

EFFECT OF WORK, TEMPERATURE, AND HUMIDITY ON THE METABOLISM OF A FAT INDIVIDUAL.

Temperature.	Grams per Hour.			
	Dry Air.		Humid Air.	
	CO_2 in Grams per hour.	H_2O in Grams per hour.	CO_2 in Grams per hour.	H_2O in Grams per hour.
20°	47.8	..	46.4	
28–30°	47.3	..	48.0	
36–37°	50.3	319+38 g. sweat.	60.7	269 + 266 g. sweat.

This individual was the same already mentioned, p. 103, and the explanation given there is equally applicable here. In a dry climate the same amount of mechanical work may be accomplished by a fat person at both 20° and 30° without changing the metabolism. At a temperature of 37° the metabolism rises, for the cooling power of the evaporating sweat does not seem sufficient to act through the dense covering of fat. This action is intensified in moist air, where the evaporation of water is hindered. Under these latter conditions the small amount of work was accomplished only at the expense of great discomfort and profuse perspiration.

The obese therefore work under great disadvantage in a hot, and especially in a hot and moist, climate. The profuse perspiration explains their desire for water to drink.

In the early experiments of Pettenkofer and Voit, already cited, it was shown that work did not raise the protein metabolism even in starvation, and that the source of the power appeared to be the increased combustion of the non-nitrogenous fat.

In other experiments a slight rise in the nitrogen metabolism, continuing into the day following work, has been noted. The protein metabolism, however, is not sufficient to yield the

energy necessary for a hard day's work. In the well known experiments of Fick and Wislicenus[1] the authors climbed the Faulhorn, in Switzerland, a mountain 1956 meters high. The product of their weight into the height to which they raised themselves gave them the work done. The experimenters took their last nitrogenous food seventeen hours before starting on their walk. They climbed for six hours and collected the urine of this period and that of seven hours thereafter. Their results were as follows:

	Urinary N of 13 hrs.	Dynamic Value of N in Kgm.	Body Weight.	Height of Faulhorn.	Work in Kgm.
Fick.....	5.74	63,378	66	1956 meters.	129,096
Wislicenus....	5.54	61,280	76	1956 meters.	148,656

The work accomplished represents three times the energy liberated from the protein metabolism of the time. The output of energy as measured above was not all the increase in the amount of mechanical energy during the period, for the heart and respiratory muscles acted with greater force, and energy was expended by swinging the arms and by friction on the road.

The fact observed by Pettenkofer and Voit that protein metabolism may not be appreciably affected during mechanical work has been abundantly confirmed by Krummacher.[2] A porter weighing 79 kilograms was given a diet containing 3700 calories, 14.28 grams of protein nitrogen and a large amount of carbohydrate. The man turned a dynamometer and produced 402,000 kilogrammeters of work. The slight increase in protein metabolism could have yielded but three per cent. of the energy required for the work. Krummacher states that protein metabolism may increase during work only when the

[1] Fick and Wislicenus: "Myothermische Untersuchungen," 1889.

[2] Krummacher: "Zeitschrift für Biologie," 1896, Bd. xxxiii, p. 108.

non-nitrogenous fat and carbohydrates become less available in metabolism. We have already seen that protein metabolism rises in the absence of carbohydrates. It may be that with the exhaustion of carbohydrates during exercise, a period ensues when the loss of their influence leads to an increased protein destruction. The larger the quantity of carbohydrates given the less marked would be this influence. It is interesting in this connection that soldiers when starting on a march may have a high respiratory quotient (indicating the combustion of carbohydrates) which falls at the end of the march (fat combustion) and which may remain lower than at first, even on a day following the march.[1] The fact that mechanical work may be accomplished at the expense of an increased combustion of fat and carbohydrates should not cause one to forget that protein *may* become the sole source of energy in the body. It has already been shown that a fasting animal, after burning all his fat, maintains his life on protein alone (p. 73), and that Pflüger kept a dog in active condition on meat alone. As protein may yield 58 per cent. of sugar, this substance may still be the principal source of energy.

The following experiment not only indicates the fully proved point that muscular work does not increase protein metabolism but it also shows that *the character of the protein metabolism is unchanged by muscular activity.* Shaffer[2] has given a man a diet which was free from purins and which contained only 5.9 grams of nitrogen. The individual spent the greater part of six days in bed as a rest period (I). He then occupied himself for five days with laboratory work, which gave a normal period (II). During a final period (III) of four days he worked in the laboratory and performed in addition such mechanical work as that of walking ten miles. The average of the analyses of the urines of the three periods are given below.

[1] Zuntz and Schumburg: "Physiologie des Marsches," 1901.

[2] Shaffer: "American Journal of Physiology," 1908, vol. xxii, p. 445.

UNCHANGED CHARACTER OF THE URINE AFTER MUSCULAR WORK.

Period.	Food.		Urine.					
			Nitrogen as:					Sulphur:
	N	Calories.	Total.	Ammonia.	Creatinin.	Uric Acid.	Rest.	Total.
I. Rest	5.9	2300	4.77	0.35	0.605	0.11	0.35	0.438
II. Normal	6.0	3000	4.40	0.38	0.60	0.106	0.42	0.424
III. Work ..	5.9	3200	3.94	0.42	0.56	0.12	0.42	0.414

Shaffer concludes that if sufficient food be allowed, an increase or decrease of muscular activity has no effect on protein metabolism as indicated by the various quantities of nitrogenous end-products which appear in the urine. Shaffer agrees with Hoogenhuyze and Verploeg[1] that with adequate nourishment the creatinin elimination is unaffected by muscular work.

Bornstein[2] reports continual retention of ingested protein during seventeen days' work, at a time when only protein was administered. The quantity of protein given was large, containing 19.96 grams of N, and the daily work accomplished was moderate, being 17,000 kilogrammeters. The nitrogen retention amounted to 1.475 grams daily, or an addition of 800 grams of "flesh" to the body in seventeen days.

Loewy[3] reaches the same conclusion that long continued muscular exercise favors protein retention. This suggests the basis of muscular hypertrophy due to physical exercise.

Large protein ingestion, however, is not apparently essential to the full maintenance of physical power. This has been shown by Chittenden,[4] who maintained soldiers and athletes in physical

[1] Hoogenhuyze and Verploeg: "Zeitschrift für physiologische Chemie," 1905, Bd. xlvi, p. 415.

[2] Bornstein: "Pflüger's Archiv," 1901, Bd. lxxxiii, p. 540.

[3] Loewy: "Archiv für Physiologie," 1901, p. 299.

[4] Chittenden: "Physiological Economy in Nutrition," 1905.

training for months at a time on diets containing between seven and ten grams of nitrogen, or about half what the average man takes if the question be left to his taste (see p. 213).

It is evident that the power to accomplish muscular work is not usually derived from protein metabolism, but from the combustion of the non-nitrogenous sugar and fat.

Therefore, physical exercise requiring fat consumption without concomitant destruction of protein must be of the greatest value in the treatment of obesity.

The problem at once arises: What is the relative value of fats and carbohydrates as fuel for the production of mechanical energy by the body?

Zuntz,[1] from experiments made by Heineman, calculates that when carbohydrates predominate in a man's diet an amount of energy above the resting requirement is liberated which equals 9.33 calories for every kilogrammeter of work accomplished, whereas when fat is given 10.37 calories are liberated in the performance of the same amount and the same kind of work. The work was done by turning the wheel of an ergostat. Since one kilogrammeter is the mechanical equivalent of 2.35 calories, it is evident that 25 per cent. of the total excess of energy developed by work is convertible into mechanical effect, the balance being dissipated as heat. Similar experiments made by Zuntz on himself showed that 9.39 and 9.33 calories of metabolism were liberated on a fat diet, 10.37 and 10.41 on a carbohydrate diet, when one kilogrammeter of work was accomplished.

There seems to be little difference in the efficacy of the body as a machine, whether fat or carbohydrates are used as fuel.

Heineman[2] remarks that Chauveau's idea that fat must be first converted into sugar before being available for mechanical work can scarcely be valid, for such a conversion of fat carbon into sugar would entail a minimum loss of energy available for mechanical work of 29 per cent.

[1] Zuntz: "Pflüger's Archiv," 1900, Bd. lxxxiii, p. 557.

[2] Heineman: *Ibid.*, p. 476.

Atwater and Benedict[1] thought that they had confirmed these results, although unfortunately the diets provided were not strictly protein and carbohydrate-protein, but were really mixed diets.

Thus J. W. C., during two periods of twenty-two days each, ingested day by day diets which produced the following metabolism as calculated from the body's excreta:

CALCULATED METABOLISM.

	PERIOD I. CARBOHYDRATE DIET.	PERIOD II. FAT DIET.
Protein	434 calories.	489 calories.
Fat	1288 "	3190 "
Carbohydrates	3371 "	1465 "
Total metabolism	5093	5144

The average of work accomplished and body heat evolved each day, as measured in the Atwater calorimeter, were as follows:

WORK AND METABOLISM AS DIRECTLY MEASURED.

	CARBOHYDRATE DIET.	FAT DIET.
Mechanical work	543 calories.	550 calories.
Body heat	4593 "	4555 "
Total metabolism	5136	5105

The work was done on a stationary bicycle. It is evident that the work could not have been at the expense of protein metabolism. But it is also plain that the work could have been derived from carbohydrate combustion even on the "fat" diet of Period II.

These experiments, however, were the first to demonstrate exactly that mechanical work was done at the expense of a dynamic equivalent of metabolism,—a splendid confirmation of the law of the conservation of energy.

In one other experiment Atwater and Benedict calculated for J. W. C. a metabolism amounting to 9981 calories, divided as

[1] Atwater and Benedict: "Experiments on the Metabolism of Matter and Energy in the Human Body," 1903, U. S. Dept. of Agriculture, Bulletin 136.

follows: Protein, 478 calories; fat, 7744 calories; carbohydrates, 1759. The man worked for sixteen hours on the bicycle. The work done measured an equivalent of 1482 calories; the body heat production was 7382 calories, both of which were measured in the Atwater calorimeter, and the total energy loss reached 9314 calories,[1] a height of metabolism attained also by Maine lumbermen[2] actively employed (p. 221).

Later work by Benedict and Carpenter[3] includes an experiment upon a professional bicycle rider, who rode the stationary bicycle in the respiration apparatus. The results per hour may be thus expressed:

	Calories per Hour.
Metabolism during rest	92.
" " work	619.
Increased metabolism due to work	527
Heat equivalent of work accomplished	112
Mechanical efficiency in per cent. ($\frac{112}{527} \times 100$)	21.3%

The rider was hard pressed and working at a maximum during this effort. One may calculate the mechanical work accomplished as being 13 kilogrammeters per second. If this work can be compared to the work accomplished by bicycle riders in a six-day competition when the individual sometimes remains on the track for 23 out of the 24 hours it may be seen that the metabolism in such cases may readily exceed 10,000 calories daily.

Although the work accomplished by the professional rider amounted to double and treble that accomplished by four less experienced individuals, the mechanical efficiency of the different riders hardly varied from the general average of 20.8 per cent. This recalls the statement of Johansson and Koraen (see p. 202) that the increased output of carbon dioxid due to

[1] The calories calculated from the metabolism and those directly measured by the calorimeter did not exactly agree in this particular instance—an exception in a brilliant series.

[2] Woods and Mansfield: U. S. Dept. of Agriculture, 1904, Bulletin 149.

[3] Benedict and Carpenter: U. S. Dept. of Agriculture, Office of Experiment Stations, Bulletin 208, 1909.

mechanical work is always directly proportional to the work accomplished.

Although from Zuntz's work it seems proved that, in furnishing power for mechanical work, carbohydrates and fat are replaceable one for the other according to their dynamic values, there is a well-founded belief that work may be obtained in larger quantity from an individual if carbohydrates be available.

Schumburg[1] finds that ingestion of carbohydrates enables a fatigued muscle to contract more powerfully. Hellsten[2] states that in doing mechanical work in the morning before breakfast, an improved capacity occurs thirty to forty minutes after ingesting sugar.

The ready exhaustion of diabetics who cannot burn dextrose confirms this observation.

Lee and Harrold[3] have found evidences of great fatigue in the excised muscles of a cat from which the readily combustible sugar had been removed by rendering the cat diabetic with phlorhizin. Another cat similarly treated, the body of which, however, had been flooded with sugar by ingestion before the animal was killed, showed a much larger capacity for muscular contraction.

The writer[4] while injecting phloretin solutions into the jugular vein of fasting rabbits, diabetic through phlorhizin, noticed that seven out of eight rabbits had convulsions, while normal rabbits were not so affected. Four died and three lost motor control of the muscles of their limbs. In these three there was an increased dextrose elimination in the urine on account of the passage of the glycogen content of the organs into the blood, which glycogen would normally be immediately available for muscular activity (p. 79). The animals which survived the convulsions obtained control of their muscles

[1] Schumburg: "Archiv für Physiologie," 1896, p. 537.

[2] Hellsten: "Skan. Archiv für Physiologie," 1904, Bd. xvi, p. 139.

[3] Lee and Harrold: Proceedings of the American Physiological Society, "American Journal of Physiology," 1900, vol. iv, p. ix.

[4] Lusk: "Zeitschrift für Biologie," 1898, Bd. xxxvi, p. 109.

in two to four hours. This indicates a slow preparation from fat of materials available for the production of muscle work.

Schumburg[1] finds that coffee and tea have no recuperative power over the muscles of a fatigued organism, except when taken with other foods, and that the stimulating action of alcohol is only temporary. Hellsten,[2] exercising before breakfast, finds that the effect of taking tea is almost negligible, and that the effect of alcohol is at first to increase the muscle power, but that after twelve to forty minutes there is a decrease in power which lasts for two hours. No such depression occurs after taking sugar. It is obvious that alcohol is not beneficial when muscular work is to be accomplished.

The carbon dioxid produced as a result of mechanical work is quickly eliminated through the lungs. Higley and Bowen[3] find that the increased elimination begins twenty seconds after the commencement of bicycle riding and reaches its maximum in about two minutes. At this point it remains constant from minute to minute provided the same amount of work is done. This principle has been frequently demonstrated by Zuntz and his pupils. It is evident, however, that the quantity of carbon dioxid excretion for the unit of work accomplished will be less during starvation and on a fat diet than when carbohydrates are ingested, by reason of the higher heat value of fat carbon.[4]

Johansson and Koraen[5] have caused a man to raise a weight of 21.7 kilograms one half meter high, each movement lasting one second and there being in different experiments 300, 600, 720, and 900 movements per hour. In the trained individual the quantity of increase in the carbon dioxid expired was exactly proportional to the number of the movements in the unit of

[1] Schumburg: *Loc. cit.* [2] Hellsten: *Loc. cit.*

[3] Higley and Bowen: "American Journal of Physiology," 1904, vol. xii, p. 335.

[4] Johansson and Koraen: "Skand. Archiv für Physiologie," 1902, Bd. xiii, p. 251.

[5] Johansson and Koraen: "Skandin. Archiv für Physiologie," 1903, Bd. xiv, p. 60.

time. The experiments were performed when food was absent from the intestines.

It has already been shown that 25 per cent. of the total energy of the increase above the resting metabolism as caused by work is converted into mechanical energy by a person turning the wheel of an ergostat with his arms.

Katzenstein[1] has shown a still more economical utilization of the fuel when the work accomplished is climbing, about 35 per cent. of the total increase in metabolism being then converted into mechanical effect. Walking, the commonest muscular exercise, is accomplished with the greatest mechanical efficiency.

A great many interesting details have been worked out in Zuntz's laboratory by his pupils. The following epitome of long investigations shows the comparative energy equivalents necessary for dog, horse, and man to move one kilogram of body weight one meter with a given rapidity along a horizontal plane or to lift one kilogram of body weight one meter high.[2] The experiments were made by placing the individual on a moving platform, the speed and incline of which could be varied.

A study of the table on p. 204 will show that it requires much less energy for a horse to move one kilogram of his weight one meter horizontally than for a dog to do the same at the same velocity. It also appears that a man of small weight requires more energy to a unit of substance than a man of large size. This rule has been confirmed in dogs by Slowtzoff,[3] who shows that energy amounting to 0.529 kilogrammeter is required for one meter horizontal motion by a dog weighing 37 kilograms, and 1.138 kilogrammeters by a dog weighing 5.5 kilograms. Slowtzoff does not find that this variation is proportional to the skin area of the animal.

The table also shows that there is little variation in the dog,

[1] Katzenstein: "Pflüger's Archiv," 1891, Bd. xlix, p. 379.
[2] Frentzel and Reach: *Ibid.*, 1901, Bd. lxxxiii, p. 494.
[3] Slowtzoff: "Pflüger's Archiv," 1903, Bd. xcv, p. 190.

horse, and man in the amount of energy necessary to raise one kilogram of body substance one meter high.

ENERGY REQUIREMENTS OF DIFFERENT ANIMALS IN PERFORMANCE OF THE SAME AMOUNT OF MECHANICAL WORK.

Animal.	Weight.	Energy Requirement in Kilogrammeters.		Velocity in Meters per Minute of Horizontal Movement.	Incline of Road in Per Cent. During Climbing Experiment.
		For moving horizontally 1 Kg. 1 Meter.	For raising 1 Kg. 1 Meter High.		
Dog	26.9	0.495	2.954	78.57	17.2
Dog	26.9	0.501	3.259		
Horse	456.8	0.137	2.912	78.57	10.3
Man	55.5	0.334	2.857	74.48	9.6–13.3
"	72.9	0.217	3.190	71.32	6.5
"	67.9	0.211	3.140	71.46	
"	80.0	0.288	3.563	51.23	30.7–62.
"	88.2	0.263	3.555	42.34	
"	72.6	0.284	2.913	62.04	23–30.5
"	81.1	0.231	2.921	60.90	
"	80.0	0.244	2.729	56.54	
F. Normal locomotion	86.5	0.219	2.746	66.94	23.3
F. Slow locomotion	86.5	0.233		35.92	
R. Normal	65.8	0.230	2.846	63.95	
R. Slow	65.8	0.251		34.58	

It is possible to calculate the food ration for a march if the figures given in the table be employed. If it be assumed that a man weighing 70 kilograms travels 74.4 meters a minute, he will accomplish 4.46 kilometers or 2.7 miles per hour. If it requires the energy equivalent of 0.217 kilogrammeters to move one kilogram of his weight one meter, it will require 67,747 kilogrammeters ($0.217 \times 70 \times 4460$) to move him 4.46 kilometers,—67,747 kilogrammeters being equivalent to 159.205 calories. This is the equivalent of 17.1 grams of fat, which may be added to the maintenance resting dietary requirement to supply the energy necessary for an hour's quiet walk on a level road. If

the road be inclined so that the man raises himself 500 meters during the hour's walk, the metabolism will be still further increased. The work of ascent will be his weight multiplied by the height of his climb, or 35,000 kilogrammeters. The expenditure of energy by the body in order to accomplish this work is threefold the work done, or 105,000 kilogrammeters, which equals 246.75 calories, or 26.5 grams of fat. The hour's walk in this case would require the production of an energy equivalent, above the resting metabolism, amounting to that contained in 43.6 grams of fat,—that is, 17.1 grams for a forward locomotion of 4.46 kilometers and 26.5 grams to lift the body to an altitude of 500 meters.

In the last-mentioned table it is seen that there is an increase in the metabolism for a unit of horizontal motion when the progress of the individual is very slow. This is explained by the fact that speed of progress was half the normal, was unusual, and forced.

The rule is that the metabolism increases with speed in men (0.39 to 0.84 per cent. per meter increase between 60 and 100 meters per minute) and in horses (1.03 per cent. per meter increase above 78 meters per minute), but this is not seen in dogs.[1]

Katzenstein[2] finds that the metabolism during the descent of a mountain is less by 10 per cent. than the increase caused by walking on a level surface. The muscles which act to inhibit a too rapid descent are not required to be so active as those which give forward impetus to the body on a level road.

This idea has recently been still further investigated by mountaineers[3] who compared the actual heat production with the energy of metabolism during one minute, for horizontal motion, and for ascent and descent of a mountain path which had a 25 per cent. incline. The results were as follows:

[1] Zuntz: "Pflüger's Archiv," 1903, Bd. xcv, p. 192.

[2] Katzenstein: *Loc. cit.*, p. 376.

[3] Zuntz, Loewy, Müller, and Caspari: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," 1906.

	Ascent 28.8 Meters.	Horizontal 100 Meters.	Descent 76 Meters.
Calories of energy of metabolism	69.3	67.8	40.8
Calories of heat liberated	46.9	67.8	85.5

The smallest liberation of heat occurred during the ascent of the mountain at the time when the energy of metabolism was being converted into energy of position.

The largest heat production occurred during the descent of the mountain. The metabolism was the least, but energy of position was converted into heat through the vibration of the body at each footfall.

Zuntz and Schumburg[1] show that a well-placed knapsack is carried by a soldier with very little increased expenditure of energy. A soldier weighing 74.45 kilograms, moving at the rate of 74.4 meters per minute, requires 541.8 calories for the movement of one kilogram of substance 1000 meters. The same soldier, laden with a knapsack weighing 19 kilograms (total weight = 93.45 kilograms), requires only 502.3 calories to move one kilogram 1000 meters. A pack may therefore be more economically moved than the body's substance, which is an argument against obesity.

Zuntz and Schumburg find an increase in the metabolism of a marching soldier if the knapsack be badly placed, or if the body be sore and weary.

Lavonius[2] finds the maximum amount of work attainable by a trained wrestler of great reputation to be the equivalent of 30 kilogrammeters per second.

A subject of very great interest is the result of training. It is well known that if a cobbler, for example, be removed from his trade and be compelled to climb a mountain, he will at first be of little use as compared with a Swiss guide. But after constant practice the blood-vessels dilate at once in response to the needs of the muscles and the heart expends less energy; un-

[1] Zuntz and Schumburg: "Studien zu einer Physiologie des Marsches," Berlin, 1901.

[2] Lavonius: "Skan. Archiv für Physiologie," 1905, Bd. xvii, p. 196.

necessary motions with the arms and legs are diminished in number; the strain for the accomplishment of a given piece of work diminishes; the thorax enlarges to promote readier respiration; the man becomes "trained," and there may be a lessened metabolism for the fulfillment of a definite amount of work.

The experimental measurements of the efficacy of the working organism as described above were made on well-trained men, a difference on account of training having been early recognized by Zuntz.

Certain differences between the urine of trained and untrained men have already been noted (p. 68).

Bürgi[1] made some investigations upon an individual before and after training for mountain climbing. The ascents were made at different altitudes on the roadbed of mountain railways, and the carbon dioxid elimination was measured. The results are shown in the following table:

EFFECT OF "TRAINING" ON METABOLISM.

Place.	Altitude in Meters.	Incline of Road in per cent.	CO_2 Excretion per Kgm. of Work.	
			Untrained.	Trained.
Brienz.....	620	17.29	2.430	2.103
Gornergrat.....	2987	19.3	2.711	2.268
Brienz.....	690	19.0	2.251	2.063
Gornergrat.....	3021	19.3	2.445	2.117

It is evident from this that a trained mountaineer accomplishes his work at the expense of less metabolism than does the untrained. Also that at a moderately high altitude (3000 meters = 522 mm. of mercury, barometric pressure) the trained organism is as efficient for mechanical work as at the sea level; whereas the untrained man requires a much greater metabolism

[1] Bürgi: "Archiv für Physiologie," 1900, p. 509.

to accomplish a unit of work at the higher altitude than at the lower.

At still higher altitudes there is always an increase in the amount of metabolism necessary to accomplish mechanical effort, and this will be discussed in another chapter.

Another fact of importance is that the effect of training especially affects the muscles involved in the particular movement, and not those which do not contract. Thus Zuntz[1] found that a dog trained for horizontal motion on a level street required 1179 small calories to move one kilogram body weight 1000 meters and 7.668 small calories to raise one kilogram body weight one meter high. The dog was then gradually trained to ascend an incline. After two years he required only 5.868 small calories to lift one kilogram one meter, but he required 1343 small calories per kilogram for horizontal locomotion through 1000 meters. Therefore the specifically trained muscles work more economically than those which are at the time but little used.

A man trained for mountaineering will often find himself uncomfortable when walking on a level road. The mountaineer will not find the bicycle an easy means of locomotion,[2] nor will the bicyclist unscathed essay the mountain.

A benefit derived from riding a horse is the shaking of the internal organs, which is also achieved by descending a steep pathway. This may be beneficial to the life processes in such a comparatively immobile organ as the liver for example. It also appears to promote a freer evacuation of the bowels.

In swimming there is considerable respiration gymnastics.[3] The water pressure upon the thorax is the equivalent of the weight of an 8-kilogram sand-bag, which the swimmer seeks to counterbalance by increasing the pressure in his lungs through puffing with his lips. By turning over on the back the swimmer removes this respiratory influence. Cold water stimulates

[1] Zuntz: "Pflüger's Archiv," 1903, Bd. xcv, p. 200.

[2] Concerning energy expended in bicycle riding see Berg, Du Bois-Reymond and L. Zuntz: "Archiv für Physiologie," Supplement, 1904, p. 20.

[3] R. du Bois-Reymond, *Ibid.*, 1905, p. 253.

metabolism (p. 101), but the effect of the salt in ordinary sea water is certainly negligible.

There can be little doubt that exercise, especially in the open air, strengthens the organism and therefore tends to prolong life. Sometimes muscular exercise is mistakenly considered as favoring intellectual activity. Yet college presidents are not selected from the ranks of prize-fighters.

CHAPTER IX.

A NORMAL DIET.

The principles of metabolism have been sufficiently explained in the foregoing chapters to make it possible to understand the basis of a diet which shall be physiologically rational.

It has been seen that the average starvation metabolism of a vigorous man at light work and weighing 70 kilograms approximates 2240 calories, or 32 calories per kilogram. It is obvious that this quantity of energy must be contained in the daily food, and a little more to counterbalance the "specific dynamic" or heat-increasing power of the foodstuffs, if the individual is to be maintained in calorific equilibrium. It has been seen that when an average mixed diet is ingested the maintenance requirement is between 11.1 and 14.4 per cent. above the starvation minimum (p. 162). This would amount to from 2488 to 2562 calories, or from 35.5 to 36.6 calories per kilogram of body weight in the case of the individual just referred to.

Rubner[1] is authority for the following table which indicates the energy requirement of men of various weights while doing light work.

Weight in Kg.	Area in Sq. M.	Calories of Metabolism.	Calories per Kg.
80	2.283	2864	35.8
70	2.088	2631	37.7
60	1.885	2368	39.5
50	1.670	2102	42.0
40	1.438	1810	45.2

Since man through clothing shuts himself off from the reflex action of cold on the skin, the greatest factor which tends to increase his metabolism is mechanical work, and the total cal-

[1] Rubner: von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 153.

ories required is here dependent on the kind and the amount of the work accomplished. The requirements in this regard have already been discussed.

A point of great interest is that of the proper proportion in which the individual foodstuffs should be put together in making up a ration.

Voit defines a food as a well-tasting mixture of foodstuffs in proper quantity and in such a proportion as will least burden the organism. What is the proper proportion?

Voit[1] gives the following ration for the use of an average laborer, such as a soldier in a garrison,—that is, for a man at work from eight to ten hours a day: Protein, 118 grams; carbohydrates, 500 grams; fat, 56 grams. This diet contains 3055 calories.

Such a ration means the food actually ingested. It is also assumed that the foodstuffs are administered in a digestible form, and are therefore completely assimilable. It has already been pointed out in the Introductory Chapter that the feces contain no undigested protein when good food is given. It is therefore fallacious to deduct the nitrogen of the feces from the nitrogen of the ingesta in order to determine the amount of protein assimilated. Fecal nitrogen plus urinary nitrogen together represent the waste of assimilable protein nitrogen (see p. 45).

The allowance of 118 grams of protein has provoked much discussion. The original figures were obtained by Voit by averaging the protein metabolism of many laboring men. This requirement of protein was therefore obtained by the statistical method, which simply showed what the average laborer in habit destroyed. For the same class of artisan, the diet given by Rubner calls for 127 grams of protein; by Atwater 125 grams; and Lichtenfelt[2] confirms Voit's average as being the quantity of protein taken by laborers in northern Italy.

[1] Voit: "Physiologie des Stoffwechsels," 1881, p. 519.

[2] Lichtenfelt: "Pflüger's Archiv," 1903, Bd. xcix, p. 1.

For men at hard labor, such as soldiers in the field, even higher quantities of protein are commended,—by Voit, 145 grams; by Rubner, 165 grams; by Atwater, 150 grams. These figures again are based on statistics. Quite recently Woods and Mansfield[1] found that the average protein in the ration of fifty lumbermen is 164 grams.

In striking contrast to this Siven[2] at the age of thirty-one and a half years and weighing 65 kilograms, finds he can maintain himself in nitrogen equilibrium for a short period on a diet containing between 4 and 5 grams of nitrogen, or 25 to 31 grams of protein. In fact, in one experiment the food contained 4 grams of nitrogen, of which 2.4 grams only were in 15.4 grams of true protein and the balance in amino-acids and other nitrogenous non-protein matter of vegetable origin. Here nitrogen equilibrium was nearly attained, the nitrogen ingested being 4, and that excreted 4.28 grams. The food given, which was rich in carbohydrates, contained 2717 calories, or 43 calories per kilogram, and the total metabolism as estimated by respiration experiments indicated a heat production of 2082 or 32 calories per kilogram. Here was practically nitrogen equilibrium maintained at the minimum level, and a low total metabolism which was largely at the expense of carbohydrates.

It will be recalled that the quantity of nitrogen in the urine in the average fasting man who has been previously well nourished is 10 grams, a minimum which is reducible only by carbohydrate ingestion.

The experiments of Siven did not satisfy people that a low protein metabolism was compatible with continued health and strength. Munk[3] and Rosenheim[4] both found that dogs given a quantity of protein sufficient only to maintain nitrogen equilibrium gradually lost strength and became afflicted with diges-

[1] Woods and Mansfield: "Studies of the Food of Maine Lumbermen," U. S. Department of Agriculture, 1904, Bulletin 149.

[2] Siven: "Skan. Archiv für Physiologie," 1901, Bd. xi, p. 308.

[3] Munk: "Archiv für Physiologie," 1891, p. 338.

[4] Rosenheim: *Ibid.*, p. 341.

tive disturbances. These experiments fortified the idea of the benefits to be derived from a diet containing more protein than was necessary for the maintenance of nitrogen equilibrium—a *luxus* consumption. Rubner declares that a large protein allowance is the right of civilized man.

The tradition that a continued liberal allowance of protein in a diet is a prerequisite for the maintenance of bodily vigor has been dispelled by Chittenden[1] and his co-workers, of whom Mendel is the most prominent.

Professor Chittenden had suffered from persistent rheumatism of the knee-joint and determined on a course of dieting which should largely reduce the protein and the calorific intake. The rheumatic trouble disappeared, and minor troubles, such as "sick headaches" and "bilious attacks," no longer recurred periodically as before. "There was a greater appreciation of such food as was eaten; a keener appetite and more acute taste seemed to be developed, with a more thorough liking for simple foods." During the first eight months of the dieting there was a loss of eight kilograms of body weight. Thereafter for nine months the body weight remained stationary. "Two months of the time were spent at an inland fishing resort, and during a part of this time a guide was dispensed with and the boat rowed by the writer frequently six to ten miles in a forenoon, sometimes against head winds (without breakfast) and with much greater freedom from fatigue and muscular soreness than in previous years on a fuller dietary."

During the period of nine months the nitrogen of the urine was determined daily. The average was 5.69 grams. During the last two months and a half, the average elimination was 5.40 grams for a body weight of 57.5 kilograms. Experiments showed that about one gram of nitrogen was eliminated in the feces and that nitrogen equilibrium could be maintained with dietaries of low calorific values (1613 and 1549 calories = 28 and 27 calories per kilogram) containing 6.40 and 5.86 grams of

[1] Chittenden: "Physiological Economy in Nutrition," 1904.

nitrogen. These figures correspond to diets containing 40.0 to 36.6 grams of protein instead of the 118 grams honored by habit and tradition. Professor Chittenden proclaims such a diet as of the highest importance to health.

The case of Chittenden recalls a note from an early convert to the "Graham system" of vegetarianism. Sylvester Graham, in 1829, began the advocacy of moderation in the use of a diet consisting of vegetables, Graham bread (made of unbolted flour), fruits, nuts, salt, and pure water, and excluding meat, sauces, salads, tea, coffee, alcohol, pepper and mustard. The letter reads as follows:[1] "The first three months of my experiment on the Graham system was attended by a loss of 20 to 30 pounds of flesh. Some of my neighbors expostulated with me,—told me I should destroy myself by starvation, and it was even reported in a neighboring town that I had actually died from that cause. But my appetite was increasingly good and my health was increasing, and in a short time my headaches, colds, costiveness, and rheumatism left me entirely, together with my hypochondriacal and gloomy state of mind, and have not returned since, notwithstanding I have been as much exposed to wet and cold as at any period of my life."

Chittenden's experiments were not confined to an individual nor to a single group of individuals. Other experiments were made on professional men, on student athletes in training, and on soldiers under military *régime*. The daily nitrogen in the urine in periods extending from five to nine months averaged as shown in the table on p. 215 in the individuals belonging to the three groups.

At convenient periods during the experiments it was determined that the body was being maintained in nitrogenous equilibrium on the diet which gave rise to the stated amounts of urinary nitrogen (p. 182).

The professional group alleged a greater keenness for its

[1] Charles Clapp: "The Graham Journal of Health and Longevity," Boston, 1837, vol. i, p. 57.

work, the athletic group won championships in games, and the soldiers maintained perfect health and strength, many professing repugnance to meat when they were allowed it after five months of practical abstinence.

Professors and Teachers.		University Athletes.		United States Soldiers.	
Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.	Weight in Kg.	N in Urine in G.
57.0	5.69	71.0	9.37	62	7.42
70.0	6.53	61.0	10.41	59	7.03
65.0	7.43	78.0	8.88	60	7.26
65.0	8.99	83.0	9.04	58	8.17
61.5	8.58	62.0	7.47	60	8.39
		56.0	7.58	53	7.13
		73.0	10.09	71	8.91
		75.0	11.06	72	7.84
				62	8.05
				59	7.38
				55	8.25
				65	8.08
				57	8.61

Although it is possible that the alleged improved mental condition[1] may have been due to suggestion (p. 302), still the fact remains that it has been proved by Chittenden's work that the allowance of protein necessary for continued health and strength may be reduced during many months to half or less of what the habit of the appetite suggests.

It remains to be seen whether this quantity of protein in the ration, which is not greater than the body would metabolize in starvation, is advisable as a program for the whole of one's adult life.

The foods with the strongest flavors are meats, which therefore add relish to a repast, and stimulate the digestive secretions.

Chittenden believes that the large quantity of protein in an ordinary diet is due to self-indulgence. He protests against such indulgence, and thinks that a needless strain is thereby imposed

[1] Chittenden: *Loc. cit.*, p. 51.

upon the liver, the kidneys, and other organs concerned in the transformation and elimination of the end-products of protein metabolism.

Lichtenfelt,[1] on the other hand, shows that while there is no statistical difference in the height of individuals as due to occupation, still the people of southern Italy are not so large nor so well developed physically as their fellows of northern Italy. He explains this stunted growth as due to a low protein and calorific intake in the food.

Hirschfeld[2] finds that the actual ration of a German soldier contains 98 grams of protein, with no untoward results. He states that writers on economics, who believe the German populace underfed because they do not have 118 grams of protein daily, are unduly pessimistic.

Although, as has been stated, the battle-ground has been over the allowance of 118 grams in Voit's dietary, it will be surprising to many to learn that Voit himself said little on the subject. He[3] showed that a vegetarian can live in nitrogenous equilibrium on a diet containing 48.5 grams of protein and that an active working man weighing 74 kilos may get along on less than 118 grams. He discouraged the tendency to eat meat in excess. He also discouraged the practice of vegetarians who overload the digestive tract with the coarser kinds of vegetable foods which leave large indigestible residues.

It is not to be denied that 50 grams of protein (containing 8 grams of nitrogen) are apparently able to maintain the adult body machine in perfect repair. Vegetarians, fruitarians[4] (who live on fruit and nuts), and vigorous adults who largely exclude protein from the diet, are evidently able to live in health and strength upon this quantity. It must be, however, that more than this amount is advisable during growth or convalescence

[1] Lichtenfelt: "Pflüger's Archiv," 1905, Bd. cvii, p. 57.
[2] Hirschfeld: "Archiv für Physiologie," 1900, p. 380.
[3] Voit: "Zeitschrift für Biologie," 1889, Bd. xxv, p. 278.
[4] Jaffa: U. S. Department of Agriculture, Bulletin No. 132.

from wasting disease, or during the muscular hypertrophy which accompanies preliminary training for athletic effort.

Abderhalden[1] mentions the fact that since various body tissues are constructed of different proteins, therefore a large variety of amino-acids in sufficient quantity must be available for their proper replenishment. Hence, it is reasonable to assume that a considerable excess of food protein is essential to supply the special amino-products for the synthesis of the characteristic proteins of the blood serum and those of the different organs.

It is certain that large ingestion of protein in hot weather increases the heat production with accompanying increase in perspiration (p. 154). Meat should therefore be avoided in hot weather. In cold weather such an extra heat production may produce a pleasurable sensation of warmth. Dr. Folin, in personal conversation with the writer, said that a dietary of carbohydrates, fat, and low protein, was easily borne by an individual during the summer, but during the winter the man complained of his sensitiveness to cold when taking the same diet.

Ranke[2] describes experiments on himself (weight = 73 kilograms) during the hottest months of summer weather in Munich, at which time he partook of an ample diet, rich in protein (135 grams), containing 3300 calories,—a diet which he had enjoyed during the preceding winter. He had to force himself to eat. He was first attacked by catarrh of the stomach, from which he recovered by dieting, and subsequently became infected by diphtheria. He had formerly suffered from catarrh of the stomach while residing in the tropics. The excess of food, and especially of protein, threw an unnecessary burden upon the heat-regulating apparatus which would not have taken place had the dictates of the appetite been allowed full sway and had the ration voluntarily been reduced.

[1] Abderhalden: "Zentralblatt für d. ges. Physiol. und Path. d. Stoffwechsels," 1906, Bd. i, p. 225.

[2] Ranke: "Zeitschrift für Biologie," 1900, Bd. xl, p. 299.

From the knowledge at hand there appears to be no strongly substantiated argument why that portion of mankind living in a cool climate should not follow the general custom of taking a medium amount of protein in moderate accordance with the dictates of their appetites. Everyone knows that excessive ingestion of highly flavored meats results in jaded appetite, an automatic signal of excess.

A similar excess of food when given to dogs results in vomiting. Rubner[1] says that many years of experience with dogs leads him to believe that appetite and capacity for digestion and absorption depend on the dog's requirement for energy in his given state of nutrition. A diet which a dog will greedily devour when in a room at a temperature of 0°, he will in part refuse when at a temperature of 33°.

While the protein quantity in the diet may vary within wide limits with the taste, the purse, or the fad of the individual, the quantity of energy required by the organism is a remarkably constant factor, being 35 calories per kilogram of body weight in the average man doing light work on a mixed diet. Comparatively little of this energy is furnished by protein.

In a fasting individual, protein furnishes 13 and fat 87 per cent. of the total heat given off from the body.

In Voit's medium mixed diet designed for a laboring man, the 118 grams of protein furnish about 15 per cent. of the total of 3055 calories.

In such an experiment as Siven's, mentioned on page 212, which represents the lowest possible level of nitrogen equilibrium, the 25 grams of protein ingested furnished 100 calories out of 2717 ingested in the food, or 3.6 per cent. However, since the total metabolism was measured as 2082 calories, the protein furnished approximately 5 per cent. of this energy.

Chittenden[2] gives a dietary containing 50 grams of protein and 2500 calories as sufficient for a soldier at work. This

[1] Rubner: "Energiegesetze," 1902, p. 83.

[2] Chittenden: *Loc. cit.*, p. 254.

allows 8 per cent. of the total energy in protein. These data may be thus summarized:

	Grams of Protein in Diet.	Cal. from Protein Metabolism in per cent.	Cal. from Fat and Carbohydrate Metabolism in per cent.
Starvation	0	13	87
Voit's standard (liberal protein)	118	15	85
Chittenden's standard (reduced protein)	50	8	92
Siven's minimum	25	5	95

The energy other than that contained in protein may be given as carbohydrates or as fat. Voit allows a laborer 500 grams of starch (2050 calories) as the quantity which the intestinal canal may readily digest, and adds 56 grams of fat (521 calories) to the diet.

It has already been observed that half the energy may be given in fat and half in carbohydrates without affecting the carbohydrate power of economy over the protein metabolism (p. 181).

This part of the subject really becomes a mere matter of calculation of the requirement of the resting organism, and the addition thereto of sufficient energy to accomplish the mechanical work.

How this is done has already been set forth in another chapter. A bicyclist riding for sixteen hours may have a metabolism amounting to 9000 calories daily, and the average ration of a Maine lumberman may rise to a value of 8000 calories. Champion wrestlers in a world's contest[1] may ingest daily during their periods of effort diets containing protein 217.9 grams (35.1 grams of N); fat, 259.5 grams; carbohydrates, 431 grams; together, 5070 calories: or protein, 182.2 grams (29.2 grams N); fat, 204.6 grams; carbohydrates, 392.3 grams; together, 4254 calories. Much cream was taken by these last-named individuals.

Chittenden[2] has fallen into error in the commendation of 2500 to 2600 calories as an ample diet for a soldier at drill.

[1] Lavonius: "Skan. Archiv für Physiologie," 1905, Bd. xvii, p. 196.

[2] Chittenden: *Loc. cit.*, p. 254.

For himself, pursuing a sedentary life, Chittenden prescribes 2000 calories or 35 per kilogram, while Mendel requires 2448 calories, or 35.3 calories per kilogram. These are entirely normal values for people at light work. In the earliest calculations of Voit, in 1866, it was shown that a man of 70 kilograms on a medium mixed diet, produced 2400 calories, or 34.3 calories per kilogram; and Rubner allows 2445 calories to men of 70 kilograms weight engaged in occupations involving light muscular work,—such men as writers, draughtsmen, tailors, physicians, etc. But the soldiers under Chittenden were put for two hours in the gymnasium, then apparently drilled for one hour, and walked another hour. This physical work requires increased energy from metabolism. It has been shown that to walk 2.7 miles in an hour on a level road requires an increased metabolism of 159.2 calories in a man weighing 70 kilograms. If a soldier during four hours actually expended this equivalent mechanical energy in excess of the amount of Professor Mendel in his laboratory, then his metabolism would be larger than Professor Mendel's by 637 calories, or he would have a total metabolism of 3085.

In Chittenden's experiments there was no analysis of the expired air, and conclusions are drawn from the maintenance of body weight.

Several of the larger sized soldiers (those who weighed 70 kilograms) lost between 3.5 and 8.5 kilograms of body weight during the experiments. Fritz, weighing 76.0 kilograms, lost 3.6 kilograms in five months. Had this all been fat, one can estimate that its heat value would have been 33,480 calories, or an available daily combustion of body substance equal to 223 calories. Conclusions drawn from weight alone can be of only the roughest character (see p. 73).

For ordinary laborers working eight to ten hours a day—such as mechanics, porters, joiners, soldiers in garrison, and farmers—3000 calories does not seem an excessive quantity.

Rubner's diet calls for 2868 calories. Chittenden's allow-

ance (2500-2600) is too low, while Atwater's (3400) appears excessive.

A third class are men at hard labor, such as soldiers in the field, shoemakers, blacksmiths, etc. For these Voit allows a dietary containing 3574 calories; Rubner 3362 calories; and Atwater 4150 calories. The differences in these figures are merely differences in the quantity of work alone.

In almost all the rations given, carbohydrates do not exceed 500 grams. The remainder is made up of fat.

Atwater[1] reports the following dietaries for farmers:

	Calories.
Farmers in Connecticut	3410
" " Vermont	3635
" " New York	3785
" " Mexico	3435
" " Italy	3565

To this list may be added for farmers in Finland 3474 calories as found in the exhaustive studies of Sundström.[2] Sundström states that the diet of the average Finnish peasant contains 136 grams of protein, 83 grams of fat, and 580 grams of carbohydrates, which corresponds to a division of calories so that protein furnishes 15 per cent., fat 21 per cent., and carbohydrates 64 per cent. of the total. He notes that if the peasant's requirement of energy were taken in rye bread alone 124 grams of protein would be ingested with it, whereas if a milk diet covered the requirement 195 grams of protein would be taken. He therefore sees no outlook for a low protein dietary among the poorer classes.

Woods and Mansfield[3] report a dietary study of a camp of fifty Maine lumbermen actively engaged in chopping and yarding logs. The investigation continued for six days. The daily average ration per man was as follows: Protein, 164.1 grams; fat, 387.8 grams, carbohydrates, 982.0 grams; calories, 8083.0. This dietary would appear almost fabulous were it not for

[1] Atwater: Report of Storr's Agricultural Station, 1902–03, p. 135.

[2] Sundström: Untersuchungen über die Ernährung der Landbevölkerung in Finland, 1908.

[3] Woods and Mansfield: *Loc. cit.*

the fact that Atwater has actually shown that a metabolism equivalent to 9300 calories a day may be produced by a man riding a stationary bicycle for sixteen hours.

A lower ration than the lowest here mentioned may be allowed to one who is confined to his bed (p. 82). In many hospitals, however, it has been found that liberal feeding of the very poor is often better than medicine.

The "standard" dietaries are given below, not because they are inflexible requirements in any sense of the word, but merely for the convenience of the reader. The individual standard will ever be controlled by climate, the amount and kind of mechanical effort; by appetite, purse and dietetic prejudice.

STANDARD DIETARIES FOR A MAN OF 70 KILOGRAMS.
(Weights in Grams.)

	Voit.	Rubner.	Atwater.
Light work:			
Protein	..	123	100
Fat	..	46	*
Carbohydrates	..	377	*
Calories	..	2445	2700
Medium work:			
Protein	118	127	125
Fat	56	52	*
Carbohydrates	500	509	*
Calories	3055	2868	3400
Hard work:			
Protein	145	165	150
Fat	100	70	*
Carbohydrates	500	565	*
Calories	3574	3362	4150

* Carbohydrates and fats to make up the fuel value.

Rubner[1] cites the following food values consumed daily per inhabitant of different cities, based upon municipal statistics of gross consumption:

MUNICIPAL FOOD STATISTICS.

	Protein. (Grams.)	Fat. (Grams.)	Carbohydrates. (Grams.)	Calories.
Königsberg	84	31	414	2394
Munich	96	65	492	3014
Paris	98	64	465	2903
London	98	60	416	2665

[1] Rubner: Von Leyden's "Handbuch der Ernährung," 1903, Bd. i, p. 160.

In contrast to this comparative uniformity hospital dietaries, as regulated by the management of such institutions, vary greatly.

Rubner[1] cites the following hospital dietaries:

HOSPITAL DIETARIES.

	Protein. (Grams.)	Fat. (Grams.)	Carbohydrates. (Grams.)	Calories.
Munich	92	54	157	1381
Augsburg	94	57	222	1823
Halle	92	30	393	2267
England	107	69	533	3266

The population of a city will ordinarily sustain itself in accordance with its needs. In public institutions, however, such as poorhouses, prisons, asylums, hospitals, and in military and naval establishments, scientific knowledge of the needs of the individual becomes a very important consideration. The prolonged endurance of an army of soldiers is just as dependent on an ample army ration as is the battleship dependent on its supply of fuel. Not only the quantity of the food makes for the well-being, but it must taste well. No amount of actual fuel value could compel the American soldiers of the Spanish-American war to eat the "embalmed beef" furnished by the Government. The flavor is to the man what oil is to the machinery of the battleship. Without flavor in the food the digestive apparatus does not run smoothly. In ordinary civilized life even psychical influences act. The cloth on the table must be spotless, and the environment inviting.

One takes as food milk, eggs, various meats, such as beef, veal, pork, mutton, fish; also cereals, such as bread, rice, corn, macaroni, beans, and peas. Sometimes alcoholic beverages are added. The calorific values of the various nutrient materials may be calculated by determining the composition of the latter by analysis and by multiplying the number of grams of each

[1] Rubner: *Loc. cit.*, p. 157.

constituent by the factor which represents its fuel value to the organism (p. 41).

As a simple illustration of this the following experiment of Rubner[1] may be cited. A man weighing 46 kilograms ate nothing but eggs for two days,—22 on the first day and 20 on the second. The 22 eggs contained 1017.4 grams of material; the 20, 878.8 grams; an average of 948.1 grams per day. Since 100 grams of egg contain 14.1 grams of protein and 10.9 grams of fat, 948.1 grams would contain a daily allowance of 133.6 grams of protein and 103 grams of fat. If Rubner's standard values for the energy content are used, the result will be as follows:

133.6 grams protein	× 4.1 =	547 calories.
103.3 grams fat	× 9.3 =	967 calories.
Total.....	=	1514 calories.
	or 33 calories per kilogram.	

This dietary of eggs was therefore nearly sufficient for the fuel requirement of this undersized individual. Notwithstanding the large amount of protein in the dietary, there was a loss of body protein equal to 7.5 grams per day.

The results of an exclusive milk diet are thus summarized by Rubner:[2] Milk (2438 grams) containing 84 grams of protein and two-thirds of the requirement of energy for the individual, produced a deposit of protein equal to 6.7 grams daily (p. 182). To cover a requirement of 2400 calories daily 3410 grams of milk would be needed, which contain 140 grams of protein. For a laboring man with a requirement of 3080 calories, 4380 grams of milk with 180 grams of protein would be necessary.

It is evident that milk with its high protein content is a food *par excellence* for the growing organism or for the invalid convalescing from wasting disease. It contains too large an amount of protein for a normal adult. A mixture of milk, toast, and

[1] Rubner: "Zeitschrift für Biologie," 1879, Bd. xv, p. 127.

[2] Rubner: Von Leyden's "Handbuch der Ernährungstherapie," 1903, Bd. i, p. 132.

cream (creamed milk-toast) may produce a modified milk diet of proper value and easy digestibility. An exclusive milk diet contains too little iron for the needs of a normal adult.

Moritz[1] recommends milk alone in treatment of obesity, in quantities varying between 1.5 and 2.5 liters daily. The normal weight in kilograms of the individual is calculated from his height, and each kilogram of such weight is provided with 16 to 17 calories in the diet, an amount which is contained in 25 c.c. of milk. Should the normal weight be 80 kilograms, 2000 grams of milk are administered daily in five portions. Such treatment brings about a considerable loss in body weight, and, although some body nitrogen is lost, a state of weakness does not ensue.

Rubner finds that 1500 grams of good white bread containing 104.4 grams of protein (=75.2 grams pure protein) will maintain a working man in nitrogenous and calorific equilibrium.

Atwater and Benedict[2] have conclusively shown that alcohol may be used in the economy in place of isodynamic quantities of carbohydrates and fats. The following table shows the average of experiments on a resting individual which lasted twenty-three days:

INFLUENCE OF ALCOHOL ON METABOLISM.

	Duration in Days.	In the Food in Grams.			Alcohol.	Cal. in Food.	Cal. of Metabolism.	Protein Balance.
		Protein.	Fat.	Carbohydrates				
Ordinary diet..	13	114	69	354		2496	2221	—2.0
Alcohol containing diet.....	10	115	47	273	72.2	2488	2221	—3.8

Atwater and Benedict employed diets containing about 2500 calories for a man at rest and 3500 for a man at work.

[1] Moritz: "Münchener medizinische Wochenschrift," 1908, July, No. 30.

[2] Atwater and Benedict: "Memoirs of the National Academy of Sciences," Washington, 1902, vol. viii, p. 231.

During the alcohol days 500 of the calories were supplied in 72 grams of alcohol, or about what is contained in a bottle of claret. The metabolism of the individual as expressed in calories was unchanged by the addition of alcohol to the diet. The alcohol was given in six small doses and 98 per cent. was burned by the organism.

On the ordinary diet 33.7 grams of fat were daily added to the body, and on the alcohol days 34.1 grams. These very valuable observations make it evident that alcohol is not a direct cause of obesity. If, however, a young man having acquired certain dietary habits at home, continues the same diet at college and begins to drink "in moderation" besides, his increasing rotundity as he returns on his vacations can be readily explained by the sparing influence of alcohol upon the fat in his diet.

A liter of German beer contains 3 to 4 per cent. of alcohol and 5 to 6 per cent. extractives. It yields 450 calories to the body, only half being derived from alcohol, the rest from the dextrin and protein-like extractives. Here is a material whose "fattening" properties may be very highly considered.

All alcoholic beverages are taken with a twofold object,—first, the desire for flavor, and second, for stimulation. Their food value, as above described, is usually little considered. In general it may be said that alcohol as a stomachic is valueless when the gastric juice is normal, but is beneficial in cases of supersecretion, hypochlorhydria, and loss of appetite. Under these circumstances small amounts of beverages containing 5 to 10 per cent. of alcohol are sufficient for all purposes.[1]

In the light of the social evils which accompany the excessive use of alcohol as a beverage there is no doubt that its total prohibition—if this were possible—would make for the public weal and improve the physical and moral condition of mankind.

The subject of alcohol could be spun out into a considerable

[1] Zitowitsch: Abstract in "Biochem. Centralblatt," 1905, Bd. iv, p. 574.

story, but for further details the reader is referred to other sources.[1]

To arrange a proper dietary for a given individual or group of individuals the very complete and valuable tables of Atwater will be found most practical. They are placed in an appendix at the end of this volume for the benefit of the student who may desire to apply in practice his knowledge of the general laws of metabolism.

Underfed or overfed individuals may alike become objects of commiseration and proper subjects for rehabilitation.

[1] The Use of Alcohol in Medicine: F. G. Benedict, A. R. Cushny, S. J. Meltzer, Graham Lusk, "Boston Medical and Surgical Journal," 1902, vol. cxlvii, p. 31; Bibliographie der gesammten wissenschaftlichen Literatur über den Alkohol und den Alkoholismus, 1904, by Emil Abderhalden.

CHAPTER X.

THE FOOD REQUIREMENT DURING THE PERIOD OF GROWTH.

"Mute and still, by night and by day, labor goes on in the workshops of life. Here an animal grows, there a plant. The wonder of the work is not less in the smallest being than in the largest." [1]

In the last chapter the average food requirement of a normal adult organism was discussed. This diet, however, may be exceeded in cases where there is a renewal of tissue following wasting disease, or where there is a development of new tissue, as during pregnancy, or afterwards during lactation, which involves the growth of the new-born infant.

Tangl[2] has reported some interesting observations on the heat production which takes place in the hen's egg incubated at 38° and 39°. Tangl called this the "energy for development" or the "ontogenetic energy." His method was to determine the calories in fresh laid eggs and to compare that amount with the calories found within the egg-shell at the moment of the birth of the chick. In this latter case the chick and the balance of egg-yolk were determined separately.

The results of these experiments showed that for the development of one gram of chick 658 small calories were used, or for the production of one gram of solids contained in a new-born chick 3425 small calories were required.

Farkas[3] has since shown that for the development from the

[1] Rubner: "Verhandlungen der Ges. der Naturforscher und Ärzte," 1908, p. 77.

[2] Tangl: "Pflüger's Archiv," 1903, Bd. xciii, p. 327.

[3] Farkas: *Ibid.*, Bd. xcviii, p. 490.

egg of one gram of silkworm larvæ 882 small calories are required, or for one gram of dry solids, 3125 small calories, figures which he compares with Tangl's for the egg.

When the whole hen's egg is considered, Tangl finds that 32 calories or 35 per cent. of the amount of chemical energy in the original egg is deposited in the body of the young embryo. The energy of development used in the production of the young chick amounts to sixteen calories or 17 per cent. of the original total. The balance or 48 per cent. of the original energy in the egg is largely found in the abdomen of the chick and is absorbed by the animal during the early days of life.

It is apparent from the above that approximately one-sixth of the energy in a hen's egg is used in the development of a chick whose body contains one-third the original energy of the egg. The other half of the energy becomes available for the chick during the first days of its life, through absorption from the intestinal wall.

Tangl finds that each egg loses in solids during incubation, and that the heat value of one gram of such solids is over 9 calories. Since one gram of fat yields 9.3 calories, the natural inference is that fat furnishes the energy for development.

Hasselbalch[1] had formerly shown that the respiration carried on by an egg indicated a respiratory quotient $\left(\frac{CO_2}{O_2}\right)$ amounting to 0.677. This low quotient points to the combustion of fat.

Tangl[2] also states that there is no loss of protein nitrogen by the egg during incubation, and that the egg-shell contributes to bone formation in the chick.

It is obvious from this work that chemical energy derived principally from the oxidation of fat is used in the development of the embryonic chick—the energy of ontogenesis. So, during pregnancy in the higher animals, not only must there be growth of the breasts, the uterine musculature, and growth of the

[1] Hasselbalch: "Skan. Archiv für Physiol.," 1900, Bd. x, p. 353.

[2] Tangl and Mituch: "Pflüger's Archiv," 1908, Bd. cxxi, p. 437; Tangl: *Ibid.*, p. 423.

embryo itself, but there must be energy expended in maintaining the new organism. Hence the appetite of the mother increases during pregnancy. Magnus-Levy[1] finds an increased requirement for oxygen on the part of the mother as pregnancy progresses. His table is as follows:

	Oxygen in c.c. per min.
Non-pregnant	302
Third month of pregnancy	320
Fourth " "	325
Fifth " "	340
Sixth " "	349
Seventh " "	378
Eighth " "	363
Ninth " "	383

Magnus-Levy estimates that of the 80 c.c. additional oxygen required during the ninth month of pregnancy, only 10 c.c. are used for the metabolism of the fetus, 20 c.c. for the increased respiratory and heart activity, while 50 c.c. are for the general needs of the maternal organism, which has increased in size and weight.

On empirical grounds von Winckel[2] for many years has used the following diet for pregnant women with, he says, "excellent results":

Protein	90 grams.	369 calories.
Fat	27 "	251 "
Carbohydrates	200 "	820 "
Total		1440 "

This certainly seems a very low ration and one hardly compatible with furnishing the full calorific requirement. It may, however, prevent an excessive growth of the child within the uterus.

Murlin[3] has made experiments on the total metabolism in

[1] Magnus-Levy: "Zeitschrift für Gynäkologie u. Geburtshilfe," 1904, Bd. lii. Also see Magnus-Levy: Von Noorden's "Handbuch des Stoffwechsels," 1906, Bd. i, p. 409.

[2] Von Winckel: Von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 469.

[3] Murlin: Proceedings of the American Physiological Society, American Journal of Physiology, 1909, vol. xxiii, p. xxxii.

pregnant dogs. From one animal a single puppy was born as the result of a first pregnancy and a litter of five from a later one. The following results were obtained:

Day from Parturition.	Date.	Excreta.		Calories of Metabolism.	
		Total N.	Total C.		
Third before	June 23	8.6	59.4	551.3	One puppy born.
First after.	June 27	8 4	65.8	640.6	Weight, 280 grams.
Nineteenth after .	July 15	5.3	51.6	505.3	Sexual rest.
Third before	Dec. 11	6.8	74.7	764.9	Five puppies born.
First after	Dec. 15	8.3	100.6	1058.8	Weight, 1560 gms.

The increase of metabolism which can be attributed to the pregnant condition may be found by subtracting the metabolism during sexual rest from that observed just before parturition. By so doing the following figures were obtained:

First pregnancy..551.3 — 505.3 = 46 calories daily for one puppy of 280 grams.
Second pregnancy..764.9 — 505.3 = 259.6 calories daily for five puppies of 1560 grams.

This extra metabolism was proportional to the weight of the puppies at birth. In the case of the first pregnancy the extra metabolism was 164 and in the second 165 calories per kilogram of puppy dog delivered three days later.

It is interesting to note that the mother and her five newly born puppies together produced twice as much heat as did the non-pregnant mother alone. The experiments were all made at a temperature of between 27° and 28°. It is evident that the puppies suckled by the mother and exposed to the outside temperature had a larger metabolism than they had had *in utero*. For the proper maintenance of the five offspring the mother with a normal metabolism of 505 calories would have to produce milk to provide for a metabolism of about 550 calories in the puppies, and still more to furnish material for their rapid growth.

Ostertag and Zuntz[1] report that a sow may yield a milk rich in fat (12.9 per cent.) and in such quantity that the energy content may amount to from two- to five-fold that required for the mother sow's metabolism.

An extraordinary phenomenon which has been observed in dogs and rabbits is that during the early weeks of pregnancy there is a loss of nitrogen from the mother's body even when the food ingested would be entirely sufficient to maintain nitrogen equilibrium under usual circumstances.[2] Jägeroos quotes Ver Ecke's description of this as "the sacrifice of the individual for the good of the species." It seems certain that the development of the fetus is accompanied by the destruction of the maternal protoplasm, perhaps, as Murlin has suggested, in order to afford hereditary building stones for the laying down of the youthful protoplasm in accordance with the type characteristic of the species.

One of Murlin's experiments (heretofore unpublished) covering the period of gestation in a dog is given below:

WEEKLY NITROGEN BALANCE IN A PREGNANT DOG.

Week.	Calories in Food per Day.	N in Diet.	N in Excreta.	N to Body
I	900	54.287	63.116	—8.83
II	976 *	56.063	60.893	—4.83
III	976	56.063	62.031	—5.97
IV	976	56.063	64.508	—8.44
V	976	56.063	62.594	—6.53
VI	976	56.063	60.064	—4.00
VII	976	56.063	54.262	+1.80
VIII	976	56.063	47.042	+9.02
IX†	976 **	32.036	25.867	+6.25

* 69.7 calories per kilogram.
** 61.0 calories per kilogram.
† Four days only.

[1] Ostertag and Zuntz: "Landwirtsch. Jahrbücher," 1908, Bd. xxxvii, p. 226.

[2] Hagemann: "Inaugural Dissertation" Erlangen, 1891; Jägeroos: "Archiv für Gynäkologie," 1902, Bd. lviii, p. 517.

This shows the large loss of maternal protein commencing immediately after conception and continuing for six weeks. Only during the last two weeks is there a marked conservation of protein as manifested in the pronounced nitrogen retention.

Some very instructive experiments have been performed to ascertain the course of the protein metabolism before and after pregnancy in women.

Zacharjewski[1] investigated the nitrogen metabolism of nine pregnant women. In three primiparæ nourished on diets containing an average of 16.5 grams of nitrogen, there was an average daily retention of 1.4 grams in the mother's organism for thirteen days before parturition. In six multiparæ the diet contained 20.66 grams of nitrogen and there was a daily retention of 5.122 grams of nitrogen during the last eighteen days of pregnancy. The figures correspond to a considerable construction of protein tissue within the organism. After childbirth there was always a loss of tissue nitrogen by the mother. In one case nitrogen equilibrium was established on the fifth day, and in another on the fourth. In six cases the loss of body nitrogen continued over a longer time. Zacharjewski says that the process of involution of the uterus is greatest during the first five to seven days after delivery, and the high nitrogen output from the mother is the result of this. After the elimination which is due to these regressive changes, there is a retention of nitrogen. This is probably attributable to the building up of the mammary glands, for Slemons[2] shows that nitrogen equilibrium, once established, was constantly maintained in a woman who did not nurse her child.

The complete record of the nitrogen elimination of a nursing mother, one of Slemons's cases, is here reproduced. It is especially instructive on account of the constancy of the quantity of nitrogen in the diet. The woman was a negress who gave birth to a healthy, vigorous child.

[1] Zacharjewski: "Zeitschrift für Biologie," 1894, Bd. xxx, p. 405.

[2] Slemons: "Johns Hopkins Hospital Reports," 1905, vol. xii, p. 121.

PROTEIN METABOLISM BEFORE AND AFTER CHILDBIRTH.

Weights are in Grams.

Days Before and After Delivery.	N in Food.	N in Urine.	N in Feces.	N in Milk.	N in Lochia.	N Balance.
11	20.5	11.9		..	..	+8.12
10	19.2	16.6		..	..	+2.07
9	18.	10.9		..	..	+6.57
8	16.9	17.1		..	..	—0.77
7	11.3	13.7		..	..	—2.95
6	19.2	13.3		..	..	+5.39
5	19.2	12.1	0.53	..	..	+6.57
4	19.2	14.1		..	..	+4.54
3	18.0	12.3		..	..	+5.12
2	14.9	12.3		..	..	+2.06
1	8.0	11.5		..	..	—4.00
Delivery	4.2	8.4		..	3.15	..
1	7.1	13.3		..	2.31	—9.66
2	13.7	13.2		0.15	1.99	—2.79
3	19.	15.8		1.04	1.61	—0.57
4	19.	18.8		1.99	1.19	—4.13
5	20.	15.6		2.02	1.05	+0.15
6	20.	21.8	1.14	2.15	1.4	—6.5
7	19.	18.1		2.02	0.84	—3.14
8	11.	16.8		2.02	0.28	—9.2
19	19.8	12.1		1.18	..	+4.89
20	18.8	15.3		1.29	..	+0.57
21	19.9	13.3		1.57	..	+3.39
22	17.3	9.7	1.6	1.58	..	+4.39
23	18.3	13.9		1.85	..	+0.68
24	18.75	11.4		2.03	..	+3.72
25	19.	15.6		1.58	..	—0.16

During the last days of pregnancy there was an average daily storage of 2.98 grams of nitrogen, and for eight days of the puerperium an average loss of 4.5 grams. Later, between the nineteenth and twenty-fifth days after birth there was an average daily storage of 2.52 grams of nitrogen. This may have been for the purpose of increasing the size of the breasts. It must be remembered that even during the period of involution an increase in the mammary glands may have been taking place at the expense of protein derived from the uterus. So the debit balance of nitrogen during this period may not represent all the protein change taking place.

The mother had plenty of milk and the baby gained an average of thirty grams a day during the first forty days of his life.

Slemons remarks that the low protein metabolism as indicated by the urinary nitrogen of the period of settled lactation is a proof that there can be no important production of milk fat from protein.

In the above experiment it will be noticed that the nitrogen of the milk is small in quantity as compared with the urinary nitrogen. On a strictly vegetarian diet the relation would change. Thus Voit[1] found 48.8 grams of nitrogen in the milk of a cow and 93.7 grams of nitrogen in her urine for the same period.

The influence of nutrition on the production of milk has been the object of countless investigations, but unfortunately most of these experiments have been conducted for commercial purposes on cows and goats. These animals, with their fundamental ration consisting of hay, do not allow of the ingestion of simple foods. On the other hand, the milk supply of even a large bitch is very limited in quantity and is with difficulty obtained. The writer is not aware of any systematic observations on the composition of human milk as influenced by food, although such researches would seem of great importance.

Perhaps the most valuable research which can to-day be used is an old one of Voit[2] upon a bitch weighing 34 kilograms. It confirmed the previous work of Kemmerich and of Ssubotin. The animal was given meat alone, meat and starch, meat and fat, starch alone, fat alone, and was also starved. The influence upon the milk secretion was found to be comparatively small. The research is a model of completeness, the plan of which could well be copied in an experiment on a human being.

[1] Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 122.

[2] Voit: *Ibid.*, p. 137.

A part of the results are given below:

INFLUENCE OF DIET ON THE COMPOSITION OF THE MILK OF A DOG WEIGHING 34 KILOGRAMS.

Food.				Milk.						
Day.	Meat in Grams.	Other Food in Grams.	N in Grams.	Amount in c.c.	N in Grams.	Fat in Grams.	Sugar in Grams.	Protein in Per Cent.	Fat in Per Cent.	Sugar in Per Cent.
6.....	1000	300 starch	34.	115	1.1	8.8	3.1	5.97	7.70	2.71
7.....	1000	200 fat	34.	144	1.4	10.8	3.8	6.86	7.50	2.67
8.....	1000	200 fat	34.	135	1.1	11.3	2.9	6.22	8.39	2.15
9.....	Mixed diet	....	..	151	1.4	13.9	3.4	6.37	9.22	2.24
10.....	500	400 starch	17.	138	1.2	11.3	3.8	5.83	8.19	2.78
11.....	500	300 fat	17.	168	1.6	16.5	4.2	6.06	9.83	2.52
12.....	Starv.	....	..	149	1.5	13.8	3.9	6.36	9.24	2.65
13.....	Starv.	....	..	118	1.0	12.2	3.0	5.62	10.32	2.58
14.....	....	500 starch	..	137	1.1	10.1	4.3	5.41	7.39	3.11
16.....	2000	....	68.	158	1.6	16.1	4.4	6.68	10.17	2.82
17.....	2000	....	68.	161	1.7	14.7	4.7	6.78	9.11	2.91

The largest quantity of milk as well as the richest in protein was obtained when meat or meat and fat were ingested. Curiously enough a diet of 500 grams of meat and 300 grams of fat gave milk of the same amount and quality as did 2000 grams of meat. It is usually said that a large protein diet stimulates the milk secretion; but this may also be due indirectly to the development of the gland cells.

The milk sugar content was scarcely affected by the diet, although a slight percentage increase was observed after starch ingestion.

The fat content was increased in starvation to its highest percentage. It was not very greatly affected by adding fat to a meat diet and it was greatly reduced by giving carbohydrates.

The action of fasting on the fat content of milk is better shown in the herbivorous goat. The writer[1] gave a milch goat a constant diet of hay, cornmeal, and bran, starved the animal for two days, and then continued the former diet. The fat

[1] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 42.

content of the milk was determined. The results were as follows:

Milk in c.c.	Fat in G.	Fat in per Cent.	
460	26.50	5.76	
470	25.90	5.52	
338	23.90	6.23	Starvation.
198	18.35	9.27	Starvation.
232	18.75	8.08	
298	16.30	5.47	
348	19.40	5.61	
362	22.30	6.16	
490	27.70	5.66	

In fasting, therefore, the fat content in the milk of the herbivorous goat approaches that contained in the carnivorous dog. With a return to the normal diet the fat content in goat's milk is reduced to its former level.

Morgen, Beger and Fingerling[1] find that a diet rich in carbohydrate and poor in fat produces in sheep and goats a poor milk containing little fat, although the general condition of the animals remains perfect. Addition of protein increases the quantity of the milk without changing the low fat percentage. Replacement of some of the carbohydrate with isodynamic quantities of fat, up to 0.5 to 1.0 gram per kilogram of animal, largely increases the fat content of the milk and thereby its nutritive value.

Contrary to this is Jordan's[2] statement that the amount of fat in the fodder is without influence upon the fat content of a cow's milk. Here the breed of the cow and not the diet is the determining factor. The German agricultural stations have recently reached the same conclusion. Morgen[3] states that the principal cause of the difference in the results of the experiments on cows and on sheep and goats lies in the fact that the smaller animals produce more milk for their weight than do

[1] Morgen, Beger and Fingerling: "Landw. Versuchsstationen," 1904, Bd. lxi, p. 1.

[2] Jordan and Jenter: "New York Agricultural Experiment Station," 1897, Bulletin 132; 1901, Bulletin 197.

[3] Morgen, Beger, Fingerling and Westhauser: "Landwirtschaft. Versuchsstationen," 1908, Bd. lxix, p. 295.

cows, and, therefore, the milk production is much more dependent on the food supply.

It has long been known that ingested fat may appear in the milk of an animal. Quite recently Gogitidse[1] has shown that after giving linseed oil to sheep their milk fat may contain 33 per cent. of linseed fat. He also finds[2] that the fat of linseed oil passes readily into human milk, and that the fat of hempseed, while influencing the composition of the milk, greatly depresses lactation during the period of its ingestion.

How may these various effects of diet be explained? The subject requires a knowledge of the processes going on in the mammary gland and these are not certainly known. It has been generally believed that the cells of the mammary glands undergo a fatty metamorphosis and, themselves breaking up, pass into the milk (Voit, Heidenhain). The milk under these circumstances might be regarded as the substance of an organ, made fluid.

Schäfer,[3] however, believes the process to be one of secretion similar to that in the salivary glands, where the cells prepare the special constituents and pass them on to the lumen. Thus casein, like ptyalin, may be specially elaborated within gland cells.

If this be the true explanation, the influence of food, in the writer's opinion, may be readily explained. An increased protein ingestion furnishes the digestive products of this substance in liberal quantities and may increase the activity of the gland.

The milk sugar content of the milk remains remarkably constant. Cremer,[4] for example, has shown that the percentage of milk sugar in the milk is unchanged in the cow after diminishing the sugar content of the animal by inducing phlorhizin diabetes.

[1] Gogitidse: "Zeitschrift für Biologie," 1904, Bd. xlv, p. 365.
[2] Gogitidse: *Ibid.*, 1905, Bd. xlvi, p. 403.
[3] Schäfer: "Text-book of Physiology," 1898, vol. i, p. 667.
[4] Cremer: "Zeitschrift für Biologie," 1898, Bd. xxxvii, p. 78.

To explain the fat content of the milk, the writer offers the following theory: When for any reason sufficient sugar is not oxidized in the body cells, these sugar-hungry cells attract fat. It has already been seen that the glycogen and fat content of the liver are antagonistic. Before lactation sets in, the cells of the mammary glands oxidize sugar and there is no great attraction for fat. It is believed that milk sugar cannot be formed in any great quantity before parturition, because it occurs in the urine only *post partum*.[1] That milk sugar is not formed outside of the mammary glands was demonstrated by Moore and Parker,[2] who completely removed these glands from a goat during the period of gestation, and later at the time of parturition found no sugar in the urine. Had milk sugar, which cannot be oxidized by the organism, been formed outside the glands it would have accumulated in the blood and have been eliminated in the urine. When in the process of lactation the dextrose furnished by the blood is converted into milk sugar (which cannot be burned within the organism), the mammary cell becomes a sugar-hungry cell which at once attracts fat from the blood. This theory of the writer explains the production of milk fat by the process of infiltration. The variation of the percentage of fat in the milk may be explained by the quantity of fat in the blood. During starvation the blood becomes rich in fat on account of the transportation of tissue fat to the cells. Administration of sugar at once reduces the supply of fat in the blood. But if fat be ingested with carbohydrates the blood becomes rich with this fat and affords material for a rich milk.

Administration of good cream with a substantial mixed diet is highly to be recommended for nursing mothers. The daily production of a liter of milk, which has a value of 640 calories, indicates the necessity of no small addition to the daily ration,

[1] Lemaire: "Zeitschrift für physiologische Chemie," 1896, Bd. xxi, p. 442.

[2] Moore and Parker: "American Journal of Physiology," 1900, Bd. iv, p. 239.

if the woman is to bear satisfactorily the strain of lactation. Probably this extra nourishment is best given in the form of fat.

Should the fat of the milk disagree with the infant, the trouble may be due to the kind of fat ingested by the mother. If, however, the indigestion be due to a large percentage of fat, a carbohydrate diet may be used to reduce the percentage in the milk.

A very important fact regarding the nutrition of the young is that the milk of one race is specifically adapted to the growth of the offspring of that particular race. Bunge[1] found that dog's milk had an ash of exactly the same composition as the ash of the new-born puppy. The ash of the milk was therefore perfectly adapted for the construction of new puppy tissue. It was, however, very different in composition from human, or cow's, or other milk. Only in the case of iron is the quantity lower than corresponds to the composition of the offspring, but this factor is offset by the fact that the animal when newborn is richer in iron than it is at any other period of life. Not only this, but the caseins of different milks are different in chemical behavior. And besides this, the rennin of the stomach is said to be specifically adapted for the coagulation of the casein produced by the female of the same race.[2]

Furthermore, the percentage quantity of the constituents in the milk is dependent upon the rapidity of the growth of the organism. Bunge[3] has shown this in the following comparative table:

	Time in Days for the New-born Animal to Double its Weight.	100 Parts of Milk Contain		
		Protein.	Ash.	Calcium Oxid.
Man	180	1.6	0.2	0.0328
Horse	60	2.0	0.4	0.124
Calf	47	3.5	0.7	0.160
Kid	19	4.3	0.8	0.210
Pig	18	5.6	..	....
Lamb	10	6.5	0.9	0.272
Dog	8	7.1	1.3	0.453
Cat	7	9.5	..	....

[1] Bunge: "Zeitschrift für Biologie," 1874, Bd. x, p. 326.

[2] Kiesel: "Pflüger's Archiv," 1905, Bd. cviii, p. 343.

[3] Bunge: "Lehrbuch der physiologischen Chemie," 1898, p. 118.

Camerer[1] finds that human milk, drawn three to twelve days after parturition, contains 0.2 milligram of iron (Fe_2O_3) per 100 c. c., while the later milk contains 0.1 milligram. The quantity is decreased if the environment or the condition of the mother be poor.[2] Using the customary methods of infant feeding with cow's milk, the infant obtains too little iron.

Blauberg[3] reports the following percentage absorption of the ash of cow's and human milk:

Kind of Milk.	Subject.	Per Cent. Milk Ash Absorbed.
Cow's	Infant.	60.70
Diluted cow's	"	53.72
Human	"	79.42
Human	"	81.82
Cow's	Adult.	53.20

The quantity of calcium in cow's milk is in excess of the needs of the human infant.

The absorption of the energy-containing constituents of the milk is remarkably constant. This is illustrated in the following table made from Rubner's experiments,[4] which shows the physiological utilization of the total calories of milk:

	Per Cent. of Calories Absorbed.
Human milk	91.6 to 94.0
Diluted cow's milk	90.7
Diluted cow's milk + milk sugar	92.2
Same given to stunted infant	87.1
Cow's milk given to an adult	89.8

As regards the relative composition of average cow's and human milk five and a half months after parturition, the following comparison may be made:

[1] Camerer: "Zeitschrift für Biologie," 1905, Bd. xlvi, p. 371.

[2] Jolles and Friedjung: "Arch. für experimentelle Path. und Pharm.," 1901, Bd. xlvi, p. 247.

[3] Blauberg: "Zeitschrift für Biologie," 1900, Bd. xl, p. 44.

[4] Rubner: *Ibid.*, 1899, Bd. xxxviii, p. 380. For further statistics of absorption consult Tangl: "Pflüger's Archiv," 1904, Bd. civ, p. 853.

PERCENTAGE COMPOSITION OF COW'S AND HUMAN MILK.

	Cow's.		Human.	
	I.[1]	II.[2]	I.[3]	II.[4]
Protein	3.41	3.2	1.0	1.52
Fat	3.65	3.9	3.0	3.28
Milk sugar	4.81	5.1	6.4	6.50

Or, expressed in the relative calorific value of the different constituents this comparison may be given:[5]

PERCENTAGE DISTRIBUTION OF CALORIES IN COW'S AND HUMAN MILK.

	Cow's.	Human.
	I.	I.
Protein	21.3	7.4
Fat	49.8	43.9
Milk sugar	28.9	48.7

Here, then, there are tremendous differences of composition which fact forces the conclusion that cow's milk is not to be substituted for human milk in rearing a child.

Patein and Daval[6] find that human milk after the first month of lactation contains but 0.8 to 1 per cent. of casein.

Another distinction between cow's and human milk is that the former contains but little extractive nitrogen while the latter may contain 18 to 20 per cent.[7] in that form. These nitrogenous extractives contain a considerable amount of carbon. This is probably one of the causes of the increase of the $\frac{C}{N}$ ratio (p. 36) to over one in the urine of breast-fed infants.

The large protein content of cow's milk may be bad for the child. In the first place it clots in a heavy mass in the baby's stomach; and in the second place, even though it be digested, it

[1] Rubner: Von Leyden's "Handbuch," 1903, Bd. i, p. 95.

[2] Van Slyke, "Modern Methods of Testing Milk and Milk Products," 1907. Average of 5552 American analyses.

[3] Rubner and Heubner: "Zeitschrift für ex. Pathologie und Therapie," 1905, Bd. i, p. 1.

[4] Söldner: "Zeitschrift für Biologie," 1896, Bd. xxxiii, p. 66. Average of the milk of five women.

[5] Rubner: "Energiegesetze," 1902, p. 418.

[6] Patein and Daval: "Journal de Pharm. et de Chimie," 1905, T. xxi, p. 193.

[7] Rubner and Heubner: *Loc. cit.*

is relatively much above the requirement of the organism, and its specific dynamic action increases the amount of heat produced.

If cow's milk be diluted with two or more parts of water, its protein content may approach that of human milk and its precipitation by rennin in the stomach is in the form of flakes. This precipitation of cow's casein takes place in even finer flakes when the milk is mixed with barley water, as was shown by Chapin.

Chapin's observations, in which the writer assisted, have been confirmed by White,[1] who says that this action is due to the presence of three-fourths to one per cent. of dissolved starch.

The dilution of cow's milk, however, reduces the quantity of fat and carbohydrates, and these must therefore be added to the milk in order to make a proper diet for a child.

To obtain a sufficient fat content, "top milk," rich in fat, may be taken from milk which has been standing, and may be mixed with water. Milk sugar may then be added.

Such a milk, called "modified milk," was first introduced by Rotch of Boston. Infants are brought up on it with greater success than was the case when undiluted cow's milk was given.

Human milk has a varying calorific value dependent largely on the amount of fat present. Thus Schlossmann[2] finds that the calorific value per liter of nineteen samples of milk from nineteen women averages 719 calories, with a maximum of 876 and a minimum of 567. The milks having the largest fuel value contained 5.2 to 5.1 per cent. of fat, while that having the lowest contained only 1.8 per cent.

The amount of the child's metabolism is dependent on his size. Rubner states that a baby weighing 4 kilograms produces 422 calories, an adult weighing 40 kilograms, 2106 calories. But the metabolism per unit of area is the same.

[1] White: "Journal of the Boston Society of Medical Sciences," 1900, vol. v, p. 130.

[2] Schlossmann: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxvii, p. 340.

Rubner and Heubner[1] summarize their results on the metabolism of differently conditioned children as follows:

	Weight in Kg.	Calories per Sq. Meter of Surface.
Infant of stunted growth	3	1090
" at the breast	5	1006
" on cow's milk	8	1143
" at the breast	10	1219

The metabolism in all these cases was essentially the same per unit of area.

In the last case the very noticeable amount of muscle movement and crying while the child was in the respiration apparatus increased the metabolism. Further details regarding this case give a very complete picture of the metabolism of an infant. The child weighed 4.06 kilograms at birth, and about 10 kilograms at the time of the experiment when five and a half months old. He was given his mother's milk.

The first day of the experiment the child was very uncomfortable on account of his new environment. The last day he was given only a small quantity of tea, and was therefore in a state of practical starvation. The carbon dioxid excretion on these days was as follows:

Day.	Grams of CO_2 in 24 Hours.
First	278.8
Second	219.9
Third	228.1
Fourth	231.1
Fifth	218.2

The diet on the second, third, and fourth days consisted of 1258 grams of human milk per day containing:

Total nitrogen	1.99 grams.
Fat	37.73 "
Milk sugar	80.5 "

Of the total nitrogen only 1.63 grams were contained in true protein, the rest being in nitrogenous extractives. The per-

[1] Rubner and Heubner: "Zeitschrift für ex. Pathologie und Therapie," 1905, Bd. i, p. 1.

centage composition of this milk is given on page 242. Its actual nutritive value was 634.5 calories.

The balance sheet of the respiration experiment showed the following daily result:

METABOLISM OF AN INFANT.

Day.	Food.	N in Food.	N in Urine.	N in Total Excreta.	N Balance.	C in Food.	C in Excreta.	C Balance.
		Grams.	Grams.	Grams.	Grams.	Grams.	Grams.	Grams.
2, 3, 4.	Milk	1.99	1.13	1.53	+0.46	63.7	65.8	—2.1
5.....	None	..	1.18	1.18	—1.18	..	60.8	—60.8

The infant was nearly in calorific equilibrium during the period of milk ingestion. There were 634.5 available calories in the milk and 660.5 calories produced in the metabolism.

The quantity of the protein metabolism was extremely small, being 9.6 grams according to the usual method of computation. The milk contained protein to the extent of 7 per cent. of its total calorific content. Of this only 5 per cent. was metabolized and 2 per cent. was added to the body. The metabolism of an infant may therefore be maintained on a diet in which 5 per cent. of the energy is supplied by protein and 95 per cent. by fats and carbohydrates.

The specific dynamic action of the milk was almost negligible, the metabolism being approximately the same during the period of feeding as during that of starvation. Curiously enough, the protein metabolism was the same on days of milk ingestion as in starvation. The "wear and tear" quota was covered by a "repair" quota of equal amount. (See p. 187.)

This child gained normally in weight before and after the respiration experiment, but during that time, struggling and crying prevented fat addition to the otherwise well-developed normal infant.[1]

[1] Heubner: "Jahrbuch für Kinderheilkunde," 1905, Bd. lxi, Heft 3.

W. Camerer, Jr.,[1] showed that a breast-fed infant nine months old may ingest 480 calories in the milk, produce 420 calories in metabolism and add 60 calories to his body, or 15 per cent. of the energy content of the diet. In this case 40 per cent. of the protein intake was added to the growing organism.

Rubner and Heubner[3] have reported a respiration experiment on a child seven and a half months old, nourished with modified cow's milk. The intake was 682.8 calories, the metabolism 593.2, leaving 89.6 calories or 12.2 per cent. for addition to the child's organism.

It is remarkable that a child's intuitive appetite should determine the ingestion of nutriment necessary to cover the energy requirement of his organism, and a small addition for normal development. A reduction of 15 per cent. in the intake of food would bring his prosperous growth to a standstill.

Heubner[3] says that the average normal infant requires 100 calories per kilogram of body weight for normal nutrition during the first three months of his life; 90 calories during the second three months, and 80 and less thereafter. The energy content of the food should never sink below 70 calories per kilogram, which is about the maintenance minimum.

The so-called "scientific feeding" of infants is unworthy of the name unless the calorific requirement is carefully considered. From lack of this knowledge babies are frequently systematically starved.

Oppenheimer[4] first called attention to the fact that the growth in grams of normal breast-fed children of the same age, may be nearly proportional to the quantity of milk ingested. Here the milk presumably had the same calorific value throughout the experiment although this could not be determined. The quantity of milk taken at each meal was found by weighing the infant

[1] W. Camerer, Jr.: "Zeitschrift für Biologie," 1902, Bd. xliii, p. 1.

[2] Rubner and Heubner: "Zeitschrift für Biologie," 1899, Bd. xxxviii, p. 345.

[3] Heubner: "Berliner klinische Wochenschrift," 1901, p. 449.

[4] Oppenheimer: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 147.

before and after nursing. Oppenheimer's table is here reproduced:

GROWTH IN GRAMS FOR 1 KG. MILK.

Month.	Feer's Subject.	Oppenheimer's Subject.
I	33.8	95.0
II	191.2	201.1
III	120.3	138.5
IV	102.6	103.3
V	57.7	120.8

The proportion of growth to milk given was practically the same during the second, third, and fourth months of these children's lives.

That the growth of suckling pigs may be proportional to the calorific value of the milk has been shown by work accomplished by Dr. L. C. Sanford and Dr. Margaret B. Wilson[1] in the writer's laboratory. Newly born pigs of two litters were reared on skimmed cow's milk and on the same milk fortified with two and three per cent. of glucose or of milk sugar. The experiments were continued from fourteen to sixteen days. The results obtained in these experiments are thus tabulated:

GROWTH OF SUCKLING PIGS.

	Wilson.			Sanford and Lusk.		
	Skim.	Lactose.	Dextrose.	Skim.	Lactose.	Dextrose.
Weight in grams when born	1322	1295	1485	1000	1050	1152
Weight in grams when killed	2205	2435	2471	1264	1890	2000
Growth in grams	883	1140	986	264	838	848
Growth in per cent.	66.8	88.0	64.4	26.4	79.7	73.6
Milk fed in c.c.	10925	11005	9707	6826	8836	9481
Available calories fed	4053	5216	4620	2339	3736	3972
Growth in grams per liter of milk	81	114	101	38	95	89
Growth in grams per 1000 calories fed	218	215	213	114	222	213

[1] Wilson: "American Journal of Physiology," 1902, vol. viii, p. 197.

It is seen that the growth of the pigs in grams was directly proportional to the calorific value of the food to the organism. The one exception was that of an ill-nourished pig fed with skimmed milk. This was an improperly nourished animal taking too little food and remaining behind his fellows in normal development. But that five out of six pigs of different litters, of different sizes and differently fed, should have gained in weight respectively 213, 214, 215, 218, and 222 grams per thousand calories in the food ingested seems more than a coincidence.

It may be further calculated that to form 1 kilogram of body substance containing 28.7 grams of nitrogen and 866 calories, required the ingestion of 4637 calories in the food.

A pig doubles in weight in eighteen days after birth. The pig of Dr. Wilson, brought up on skimmed milk with 3 per cent. of milk sugar added, nearly doubled in weight in sixteen days.

Comparing the fuel value of sow's milk and that of the skimmed cow's milk to which milk sugar had been added, the following results are significant. Of 100 calories in the food there are:

	Sow's Milk.[1]	Skim Milk + 3 Per Cent. Milk Sugar.
Protein	19.5	36.5
Fats	72.0	2.5
Carbohydrates	8.5	61.0

It is apparent from this that normal growth of the young organism may be attained by the replacement of fat by milk sugar in isodynamic quantity. This fact may become of importance in infant feeding.

Dr. Wilson found, when the pigs reared on these diets were killed and their composition compared with that of three pigs of the same litter which were killed at birth, that there was a retention for growth of 18 to 19 per cent. of the energy in the food. This retention of a definite nutrient factor is a necessary corollary to the fact of the growth being proportional to the calorific intake.

[1] Calculated from Ostertag and Zuntz: "Landwirtsch. Jahrbücher," 1908, Bd. xxxvii, p. 211.

In children Camerer found 15 per cent., Rubner and Heubner 12.2 per cent. so retained.

The percentage of calcium (CaO) in the dry solids of the pigs reared on the various skim milks was 8.29, 8.02, and 8.13, showing that the absorption of calcium depended on the growth of the organism, and not on a variation in the quantity ingested.

There is apparently a fixed and definite tendency towards uniform growth. Schapiro[1] found that if young kittens were chloroformed twice daily their growth was retarded in comparison with normal control animals. However on stoppage of the chloroform treatment, the greater rapidity of growth during an after period fully compensated for the earlier delay in development.

Another instance which demonstrates that the young organism may grow in proportion to the energy ingested in the food, is brought to light by calculations based on the work of E. Rost.[2] This author gave meat, fat and bone-ash to three dogs of the same litter, the experiment starting on the ninety-eighth day of their lives and continuing eighty-eight days. The writer has thus calculated the results:

	Dog I.	Dog II.	Dog III.
Weight in grams at start	3,200	2,200	4,150
Weight in grams at end	6,280	4,620	8,750
Growth in grams	3,080	2,440	4,600
Growth in per cent	96	110	110
Available calories ingested	24,420	17,336	34,276
Gain in grams per 1000 calories ingested	122	141	134

It is worthy of note that these growing dogs, fed with meat and fat, gained in weight nearly the same number of grams per 1000 calories ingested in the food. This law of growth seems reasonably established. It simply expresses the fact that during the normal development of the young of the same

[1] Schapiro: Proc. of the Physiol. Society, "Journal of Physiology," vol. xxxiii, p. xxxi.

[2] Rost: "Arbeiten aus dem kaiserlichen Gesundheitsamte," 1901, Bd. xviii, p. 206.

age and species, a definite percentage of the food is retained for growth irrespective of the size of the individual.

Rubner[1] in apparent ignorance of this work of Dr. Wilson, has arrived at essentially the same conclusions, and he finds that the law is true regarding all species (horse, calf, sheep, pig, dog, cat, rabbit) except man. He formulates the "law of constant energy expenditure" as follows: *The amount of energy (calories) which is necessary to double the weight of the newly born of all species (except man) is the same per kilogram no matter whether the animal grows quickly or slowly.* To construct one kilogram of normal body substance containing 30 grams of nitrogen and 1722 calories, 4808 calories are required except in the case of man, where six times that amount is needed.

Rubner finds in all species the constant retention of approximately the same percentage of the energy ingested, which averages 34.3 per cent., except in the case of man, where the energy retained for growth is only 5.2 per cent. He states that 40 per cent. of the energy ingested may be retained for the growth of pigs, whereas Dr. Wilson found only 20 per cent. so retained. This is because the pigs in the latter case were given skimmed milk and the added tissue substance was found on analysis to have a heat value of only 866 calories per kilogram, instead of 1722 as assumed by Rubner.

It is therefore evident that while it requires the same energy equivalent to construct one kilogram of new substance in young animals, the percentage of energy retained for growth may depend upon the amount of fat in the diet.

Rubner states that if the requirement for energy in the various animals be placed at 100, then the amount of energy in the food actually ingested by them averages 202. This corresponds to Dr. Wilson's computation of the energy ingested by the growing pigs, which averaged 2100 calories per square meter of surface, as compared with a normal *requirement* of

[1] Rubner: "Das Problem der Lebensdauer und seiner Beziehung zu Wachstum und Ernährung," 1908.

1089. Dr. Wilson explained this high energy requirement as being partly due to growth and partly to the extreme activity of the little animals. A human infant does not require this large excess of energy in his food, probably because he is kept warm and sleeps much of the time.

Finally Rubner has calculated that the quantity of energy metabolized in a kilogram of living cells from maturity to death is the same in different animals, except in the case of man, who again occupies an exceptional position.

This is represented in the following table:

	Body weight in Kg.	Length of Life in Years after Maturity.	Calories Produced Per 1 Kg. Adult Body-Substance.
Man	60.	60	775,770
Horse	450.	30	169,900
Cow	450.	26	141,090
Dog	22.	9	163,900
Cat	3.	8	223,800
Guinea-pig	0.6	6	265,500

Rubner finds that among the animals each kilogram of adult body substance metabolizes an average of 191,600 calories and then dies. Man alone has power in his protoplasm to use a much larger share of energy in the furtherance of his activities.

TABLE SHOWING FLOURENS' LAW OF LONGEVITY.

	Time in Days from Birth to Double Birth-weight.	Time in Years Until Full Growth.	Deduced Average Longevity in Years.	Maximum Recorded Longevity in Years.
Man	180	20	90–100	152–169
Camel	..	8	40	100
Horse	60	5	25	50
Cow	47	4	15–20	..
Lion	..	4	30	60
Cat	$9\frac{1}{2}$	$1\frac{1}{2}$	9–10	20
Dog	9	2	10–12	24

Bunge[1] has recently recalled the relationship between rapidity of growth and longevity, as originally suggested by Flourens in 1856. This writer believed that if the time of reaching the end of growth be multiplied by five, the average term of life might be computed. This relationship may be tabulated as shown on p. 251.

Bunge calls attention to the fact that a horse more often lives to be forty than a man to be a hundred. Either the law is false, or man is a too early victim of an improper heredity or environment.

For metabolism in youth, see page 170.

[1] Bunge: "Pflüger's Archiv," 1903, Bd. xcv, p. 606.

CHAPTER XI.

METABOLISM IN ANEMIA, AT HIGH ALTITUDES, IN MYXEDEMA, AND IN EXOPHTHALMIC GOITER.

In man one-thirteenth part of the body weight is carried as blood to the lungs at least every minute and there exposed for a period of two seconds to the action of the alveolar air. The blood in the capillaries of the lungs may be estimated as a film 0.01 millimeter in thickness, and 150 square meters in area, or nearly a hundred times the area of the surface of the body. Zuntz estimates the combined thickness of the alveolar wall and capillary wall at 0.004 mm. This is the total distance separating the alveolar air from the blood. The gaseous exchange between the air and the blood is thus readily made possible. Complete deprivation of oxygen results in asphyxiation and death.

The question arises, Will there be any effect upon metabolism if the oxygen supply for the body be reduced? Such a reduction of oxygen available for the tissues might be brought about by bloodletting, anemia, carbon-monoxid poisoning, by life on high mountains, or in balloons at high altitudes, or in pneumatic cabinets at reduced pressure, or by the artificial restriction of the free influx of atmospheric air into the lungs. Any of these methods if carried beyond a certain point is known to produce death.

It was noted by Lavoisier and confirmed by Regnault and Reiset that the respiration of pure oxygen did not increase the metabolism. Liebig was convinced that atmospheric pressure was without influence, for it was evident to him that life at the sea-level was of the same character as on high mountains. In

confirmation of these principles Zuntz[1] has recently shown that if air rich in oxygen be respired, there is an increased oxygen absorption lasting for about one minute, and then the normal quantity is absorbed. The primary increase in the quantity of oxygen absorbed is due to the filling of the lungs with oxygen and a further saturation of the blood with it, processes which are without effect on tissue metabolism. There is apparently no retention of such oxygen within the cells of the organism.

However Hill and Flack[2] show that in the fatigue of athletes oxygen inhalation increases the lasting power and decreases the fatigue, probably by maintaining or restoring the vigor of the heart. They believe that the fatigue which follows an athletic feat is mainly cardiac in origin, and due to want of oxygen.

Pflüger[3] first showed that frogs could live for a long period in an atmosphere which was free from oxygen when they were maintained at a temperature of 0°. After five hours they were capable of movement, and after seventeen hours although apparently dead they could be revived when placed in the air. Fletcher and Hopkins[4] have found traces of lactic acid in normal resting frogs' muscle, and also traces after a series of muscular contractions which were induced in an atmosphere of oxygen; but they found lactic acid in large quantity in the muscle if the contractions were brought about under anaerobic conditions.

Lesser[5] has placed frogs in an ice calorimeter and filled the chamber in which they lived first with air and then with hydrogen. When living in air the animals produced more heat and only half as much carbon-dioxid as they did when they lived in hydrogen gas. In the air each milligram of carbon dioxid exhaled corresponded to a production of 4.5 small calories; in hydrogen, to only 1.6 calories. Hence the processes taking place in the two cases could not have been the same. The

[1] Zuntz: "Archiv für Physiologie," 1903, Suppl., p. 492.

[2] Hill and Flack: "Journal of Physiology," 1909, vol. xxxviii, p. xxviii.

[3] Pflüger: "Pflüger's Archiv," 1875, Bd. x, p. 313.

[4] Fletcher and Hopkins: "Journal of Physiology," 1907, vol. xxxv, p. 247.

[5] Lesser: "Zeitschrift für Biologie," 1908, Bd. li, p. 287.

anaerobic carbon dioxid production could not have been at the expense of oxygen stored in the tissues of the frog or the heat production per unit of carbon dioxid exhaled would have been the same as in air, instead of being only 35 per cent. as much. The processes involved in this case can only be conjectured. It has already been stated that *ascaris*, an anaerobic inhabitant of the intestine, may convert glycogen into fatty acid with the elimination of carbon dioxid and the evolution of heat. (See p. 176.) Similar processes might take place in the anaerobic frog. Also a certain amount of energy is liberated when dextrose is converted into lactic acid, which equals 3.4 per cent. of that contained in the sugar. According to Zuntz,[1] any anemic condition which results in the production of lactic acid makes demands on the glycogen reserves of the body, so that sugar may rise abnormally in the blood, and both sugar and lactic acid appear in the urine.

The consideration of the subject of subnormal oxygen supply may be taken up with bloodletting, which produces an artificial anemia. Bauer,[2] in Voit's laboratory, was the first to study this systematically and found that the immediate result of bloodletting in the dog was an increased protein metabolism, but that the carbon dioxid elimination was unchanged. Eighteen to 27 per cent. of the total blood in the body was removed in these experiments.

Hawk and Gies[3] confirm the reports of a higher protein metabolism after bloodletting.

Finkler,[4] in Pflüger's laboratory, withdrew one-third of the total blood from a dog, thereby reducing the rapidity of blood-flow in the femoral artery by one-half, and yet there was no change in the quantity of oxygen absorbed, and therefore of the quantity of the carbon dioxid exhaled. Finkler noted, however,

[1] Zuntz: "Die Kraftleistung des Tierkörpers," Festrede, 1908, p. 18.
[2] Bauer: "Zeitschrift für Biologie," 1872, Bd. viii, p. 567.
[3] Hawk and Gies: "American Journal of Physiology," 1904, vol. xi, p. 226.
[4] Finkler: "Pflüger's Archiv," 1875, Bd. x, p. 368.

that the quantity of oxygen in the venous blood grew constantly less after repeated bleedings. This indicates the inter-relation between the oxygen supply and the needs of the tissues. Under ordinary circumstances there are 20 volumes per cent. of oxygen in the arterial blood, of which 12 volumes per cent. may return as an unused excess to the right heart. Repeated bleedings by Finkler reduced this percentage in venous blood from 11.80 per cent. to 8.80, 4.06, and 2.71 per cent. The carbon dioxid content of the blood remained unchanged. This decrease in the oxygen content of the blood may stimulate both the heart and respiration to compensatory activity, although nothing resembling asphyxia be present. While the total heat production is unchanged in anemia following bloodletting (except as influenced by increased cardiac and respiratory activity), still it is evident from the diminution of oxygen present in venous blood that there would not be a sufficient supply of oxygen to provide for a largely increased metabolism. Hence the anemic organism is incapable of great muscular work without quick exhaustion accompanied by rapid respiration and heart-beat. These latter are further efforts of compensation for the decrease in the oxygen-carrying elements of the blood.

After bloodletting of any considerable magnitude, lactic acid and, it is reported, a small amount of sugar, appear in the urine. Thus Araki[1] found lactic acid in the urine of rabbits which had been bled. He also found lactic acid in the urine of rabbits which had been exposed to the action of rarefied air, and he found lactic acid and dextrose in the urine of animals the oxygen-carrying capacity of whose blood had been diminished through the respiration of carbon monoxid. It should be noticed in passing that wherever lactic acid is formed in the organism there is a concomitant rise in protein metabolism. The anemic condition may possibly influence the enzyme which normally breaks up lactic acid, so that its metabolism is not effected. Since this lactic acid is a derivative of dextrose,

[1] Araki: "Zeitschrift für physiologische Chemie," 1894, Bd. xix, p. 424.

its non-combustion may raise the protein metabolism to a higher level, just as is the case when sugar remains unburned in diabetes. This is true in spite of the fact that the total metabolism, as represented by the heat of combustion of protein and fat, remains unaltered.

Another fact which has been observed by Lewinstein[1] is that when rabbits are kept in a bell-jar at a barometric pressure of 300 to 400 mm. (corresponding to 5000 to 7500 meters above sea-level) they die on the second or third day and autopsy reveals extreme fatty infiltration of heart, liver, kidney, and diaphragm. These animals took no food. The cause of this fatty change, in the present writer's opinion, was the lessened combustion of sugar or its derivative, lactic acid, which always induces an abnormal deposit of fat in any sugar-hungry cells (p. 304).

Kohler[2] artificially compressed the trachea of rabbits by tying a lead wire around it. The animals recovered from the operation and lived for four weeks in a condition of dyspnea. Appetite, weight, urine, and body temperature remained normal almost until the end. The dyspnea was apparently insufficient to affect the metabolism. Increased respiration and heart activity were effectual efforts at compensation, so that there was no lack of oxygen in the animals. However, the altered pressure in the lungs and the continued dyspnea brought about a condition of stasis of which the animal died. The secondary alterations were acute and widespread, and were hyperemia of the lungs, vesicular and intralobular emphysema of the lungs, and hypertrophy of both sides of the heart.

Pettenkofer and Voit[3] observed the metabolism in an acute case of leukocythemia of four years' duration, and at a time four months before the death of the patient. There was one white to every three red blood-corpuscles, a high degree of

[1] Lewinstein: "Pflüger's Archiv," 1897, Bd. lxv, p. 278.

[2] Kohler: "Archiv für exper. Path. u. Pharm.," 1877, Bd. vii, p. 1.

[3] Pettenkofer and Voit: "Zeitschrift für Biologie," 1869, Bd. v, p. 319.

anemia, and great physical weakness. The metabolism was exactly the same as in a normal resting man living under the same dietary conditions.

In emphysema of the lungs in man, determinations by Geppert and by Speck[1] have shown that the respiratory exchange of gases was entirely within normal limits.

It is evident from these various citations that the general oxidation of the body is normally maintained in anemia and in pulmonary disease, provided the disturbances are not of extreme intensity.

The constantly increasing use of mountain air as a recuperative force for the worn-out individual leads to the inquiry whether the metabolism at high altitudes is different from that at the sea level. For knowledge of this sort we are principally indebted to Zuntz and his pupils. The study of the subject may be taken up by using three different methods: First, the pneumatic cabinet; second, balloon ascensions; third, mountain ascents.

The pressure of the atmosphere varies with the height from the sea-level as appears in the following table:

Altitude.			Barometer
Meters.	Feet.	Miles.	in Mm. Hg.
0	0	0.	760
1000	3,281	0.6	670
2000	6,562	1.2	592
3000	9,843	1.9	522
4000	13,124	2.5	460
5000	16,405	3.1	406
6000	19,686	3.7	358
7000	22,967	4.4	316
8000	26,248	5.0	297

The relative composition of the atmosphere is the same at all distances from the earth's surface. Durig and Zuntz[2] find that the atmosphere at a height of 2900 meters contains carbon dioxid 0.03 per cent., nitrogen 79.11 per cent., and oxygen 20.86 per cent., whereas, at an altitude of 4600 meters it contains

[1] Cited by Jaquet: "Ergebnisse der Physiologie," 1903, Bd. ii, I, p. 562.

[2] Durig and Zuntz: "Archiv für Physiologie," 1904, Suppl., p. 421.

carbon dioxid 0.03 per cent., nitrogen 79.10 per cent., oxygen 20.87 per cent. These are values practically identical with each other and with those determined at sea-level.

Fraenkel and Geppert[1] placed a dog, which had fasted seven days, under the influence of greatly diminished atmospheric pressure and found an increased protein metabolism which continued on the second and third days. They also suspected the presence of products of incomplete combustion in the urine. These results accord with Araki's investigations.

Von Terray[2] finds no change in the respiratory activity of dogs in air containing between 87 and 10.5 per cent. of oxygen. When 10.5 per cent. of oxygen is present an increased respiratory activity commences. With 5.25 per cent. of oxygen there is every indication of lack of oxygen for the tissues, and the elimination of lactic acid in the urine is pronounced. The quantity of lactic acid eliminated was greatest after the respiration of an atmosphere containing 3 per cent. of oxygen. The quantities obtained were 1.206, 1.860, 2.176, 2.300, 2.352, 2.663, 3.020, and 3.686 grams of lactic acid in twenty-four hours. In these cases we again see the analogy of the metabolism to that already cited as having been discovered by Araki after bloodletting in rabbits.

L. Zuntz[3] found that when he respired in a pneumatic cabinet, at an atmospheric pressure of 448 mm. of mercury, there was no change in his respiratory metabolism as compared with the normal. The results may be tabulated as follows:

Per Cent. O_2 in Air.	Pressure in Mm. Hg.	Respired Per Minute. O_2 c.c.	Respired Per Minute. CO_2 in c.c
21	758 mm.	231.25	200.15
12	448 mm.	238.7	213.1

This latter experiment was done at a pressure corresponding to a mountain height of 4500 meters. He also showed that

[1] Fraenkel and Geppert: "Ueber die Wirkungen der verdünnten Luft," 1883.

[2] Von Terray: "Pflüger's Archiv," 1896, Bd. lxv, p. 440.

[3] Loewy and Zuntz: "Pflüger's Archiv," 1897, Bd. lxvi, p. 477.

variations in atmospheric pressure within the above limits had no effect on the metabolism during muscular exercise.

Von Schrötter and Zuntz[1] made two balloon ascents to heights of 4560 and 5160 meters. Zuntz showed an increased oxygen absorption of 7 per cent. above that at sea-level. In the case of Von Schrötter the increase was slight, except during one interval of shivering, when a 20 per cent. increase was recorded. The authors attributed the slight rise in the metabolism to the increased work done by the respiratory muscles. During the higher ascent sugar appeared in the urine of Zuntz, indicating incomplete oxidation.

A research of Zuntz[2] on the subject of mountaineering describes how he and Durig ascended to the Col d'Olen (2900 meters), and, having remained there for a week, passed upward to a hut (4560 meters) constructed near the summit of Monte Rosa, the highest mountain of the Alps after Mont Blanc. They lived in this hut two weeks and a half. The height of the barometer was 443 millimeters, which indicates a quantity of oxygen amounting to 12.2 per cent. of an atmosphere. On the Col d'Olen there was no increase in their metabolism when they were resting, and there was no increase in the requirement of energy necessary to accomplish one kilogrammeter of work. This agrees with the results of Bürgi elsewhere mentioned (p. 207). At the higher level, near the summit of the mountain, the resting metabolism increased at once and permanently to the extent of 15 per cent. Zuntz during a former sojourn had noted an increase of 44 per cent. in his metabolism when on the mountain. Exposure to the sunlight was almost without effect on the metabolism. The increased metabolism was not due to cold, for it was present when the individual was in a warm bed in the hut. At sea-level the energy equivalent of three kilogrammeters is liberated in the body in order to lift one kilogram of body substance one meter high. Here on the snow-fields of

[1] Von Schrötter and Zuntz: *Ibid.*, 1902, Bd. xcii, p. 479.

[2] Durig and Zuntz: "Archiv für Physiologie," 1904, Suppl., p. 417.

Monte Rosa Durig required the equivalent of 4.0 to 4.8, Zuntz 5.3 to 6.8 kilogrammeters of energy to accomplish one kilogrammeter of work. This agrees with a former experiment of Zuntz when he was living in the same locality, in which he found the increased metabolism necessary to effect one kilogrammeter of work in climbing was 70 per cent. above the requirement for the same work at sea-level.

That L. Zuntz (see p. 259) found no increase in his metabolism, either during rest or work, when he was in a pneumatic cabinet under an atmospheric pressure of 448 mm., is explained by Durig and Zuntz as due to the short length of the experiment.

Not only is the metabolism necessary to accomplish work greater on high mountains than at sea-level, but the capacity for work is greatly reduced. Schumburg[1] found that he could accomplish a maximum of 999 kilogrammeters of work in one minute in Berlin, 619 when on the Monte Rosa glacier, and only 354 kilogrammeters when he was on the top of the mountain. The limit of work on Monte Rosa was therefore one-third what could be accomplished in Berlin, probably on account of the accumulation of imperfectly oxidized products of metabolism, which reduces the muscular power.[2]

Durig and Zuntz, Mosso, and others, have found their respiration to be distinctly of the Cheyne-Stokes character after a return to the hut subsequent to exercise in the higher Alps. They found that when they were on Monte Rosa a temporary oppression resulted if their respiration was partly hindered,—as in the case of lacing their boots. Also, strict attention to a definite task might reduce the respiratory activity to such an extent that anemia of the brain, accompanied by dizziness, readily ensued.

Workman[3] reports that normal sleep was impossible when camping in the Himalayas at a height of 19,358 feet (nearly

[1] Zuntz and Schumburg: "Pflüger's Archiv," 1896, Bd. lxiii, p. 488.

[2] Lee: Fatigue, "The Harvey Lectures," 1905–06, p. 169.

[3] Workman: "Bulletin of the American Geographical Society," 1905, vol. xxxvii, p. 671.

6000 meters). When the individuals of the party dozed they were awakened gasping for breath. Air at this height contains 10 per cent. of oxygen.

The ventilation of the lungs of Durig and Zuntz while at rest at different altitudes varied as follows:

	Respired in Liters per Minute.		
	Zuntz. Actual.	Zuntz. Reduced to 760 Mm. Hg and 0° C.	Durig. Reduced to 760 Mm. Hg and 0° C.
Sea-level	4.61–5.03	4.15–4.53	5.00–5.63
Col d'Olen	5.97–6.36	3.99–4.16	3.81–5.07
Monte Rosa	6.86–8.52	3.71–4.88	4.05–4.60

The actual amount of inspired air appears to be about the same at different altitudes, an increased volume compensating for increasing rarefaction of the atmosphere.

The atmosphere in which one lives is really the air within the alveoli (Pflüger). Durig and Zuntz have calculated the pressure of oxygen and carbon dioxid within their alveoli at different levels, and, measured in terms of millimeters of mercury, have found them to be as follows:

	Pressures in Mm. Hg.			
	Zuntz (of Berlin).		Durig (of Vienna).	
	O_2	CO_2	O_2	CO_2
At home—rest	107	36	109	32
At home—ascending walk	109	33	99	37
On Monte Rosa—rest	57	21	53	24
On Monte Rosa—horizontal walk	60	17	55	21
On Monte Rosa—ascending walk	63	18	55	24

It is evident from a study of the results that muscular exercise in all these localities produces an increase in the alveolar tension of oxygen and a decrease in that of carbon dioxid. This is brought about by the stimulation of respiration.

It will be interesting to examine the evidence of the effect of decreasing oxygen tension on the capacity of the blood in the lungs to absorb oxygen. The usually accepted doctrine that atmospheric air, shaken with blood, will practically saturate

the hemoglobin present, rests upon Hüfner's experiments with carefully prepared solutions of hemoglobin. Loewy and Zuntz,[1] however, show that if normal blood be used the saturation is 89 per cent. at the most. On the basis of this newer work, Durig and Zuntz[2] have calculated the saturation of the hemoglobin within the blood at the different altitudes. At Berlin, oxygen exerting alveolar pressures of 113 and 103 mm. would saturate the blood in the lungs to the extent of 81.9 and 80.5 per cent., respectively. On Monte Rosa alveolar oxygen at pressures of 57.0 mm. (Zuntz) and 53.2 mm. (Durig) would respectively cause a saturation to the extent of 69.5 and 68 per cent. The lowest recorded oxygen pressure in the alveoli was 48.3 mm. (Durig), which corresponded to 65.9 per cent. of oxyhemoglobin, and was accompanied by severe headache. A quickened heart-beat produced a more rapid circulation than normal. The experimenters find no ground for believing that there was at any time any real oxygen deficiency in any of the important tissues of the body. They consider that their gradual ascent from sea-level prevented the usual disturbances of appetite and digestion which are probably caused by anemia in the abdominal region (mountain sickness).

After exercise, however, Zuntz and Durig noted qualitative changes in the metabolism indicating incomplete combustion. This was shown in the reduction of the respiratory quotient below that of fat. The authors say:[3] "The experiments leave no doubt that the increased deficiency of oxygen supply, induced by the greater metabolism of the tissue during exercise, is associated with the cause of the increased requirement of energy."

There is no reference to the presence of either sugar or lactic acid in the urine after exercise on Monte Rosa, substances whose presence one might suspect. Loewy[4] reports an in-

[1] Loewy and Zuntz: "Archiv für Physiologie," 1904, p. 207.

[2] Durig and Zuntz: *Loc. cit.*, p. 442.

[3] Autorenreferat: "Biochemisches Centralblatt," 1904, Bd. iii, p. 285.

[4] Loewy: "Archiv für Physiologie," 1906, p. 386.

creased excretion of amino-acids during mountain sickness or during exercise at these high altitudes.

It is apparent that life at an altitude of 4600 meters is on the borderland between the normal and the dyspneic. Less work can be accomplished, and this at the expense of a greater metabolism, because of the inhibition of the muscle mechanism through the accumulation of imperfectly burned products of metabolism.

Higher mountain ascents have been accomplished than the one here described. The celebrated mountaineer, Whymper, has ascended Chimborazo (6247 meters) without suffering from mountain sickness.

Boycott and Haldane[1] found in experiments on themselves when they were confined in a steel pneumatic cabinet that if the atmospheric pressure was reduced to 356 mm. of mercury, corresponding to a height of 6000 meters, the oxygen pressure in the alveoli fell to 30 mm. and pronounced cyanosis occurrec, accompanied first by loss of memory and then by unconsciousness. There was only slight hyperpnea. Greater attenuation of the atmosphere on mountains and in balloons may often be tolerated. This they ascribe to a gradual production of lactic acid within the organism which renders the respiratory center especially sensitive to the stimulus of carbon dioxid. They recommend that one frequently partake of carbohydrates when among the higher mountains in order that a maximum amount of carbon dioxid be furnished to the blood stream. The carbon dioxid pressure in the alveoli falls as an accompaniment of the rising acid content of the body. This changed condition of the blood does not pass off at once on return to a lower level.[2] The respiratory stimulus persists and the beneficial effects of descending are promptly felt. At a given altitude on the descent the alveolar oxygen pressure will therefore probably be higher than

[1] Boycott and Haldane: "Journal of Physiology," 1908, vol. xxxvii, p. 262.

[2] Ward: *Ibid.*, p. 378.

at the same altitude on the ascent on account of the greater stimulation of the respiratory center.

These relations are shown in the following table compiled from Ward's experiments on himself:

	Pressures in Mm. of Hg.		
	Barometer.	Alveolar Air.	
		CO_2.	O_2.
Lister Institute, London	769	37.7	109.0
Zermatt	633	34.2	81.6
Monte Rosa	443	28.5	49.8
Zermatt, on return	633	28.9	91.0
2 hours after	...	32.5	...

One may compare the statement of Boycott and Haldane that cyanosis occurred in them when the oxygen pressure in the alveoli fell to 30 mm. with the statement of Loewy and Zuntz[1] that when the oxygen pressure is 31.8 human blood will absorb oxygen so that 56 per cent. of its hemoglobin is saturated. This agrees well with the finding of Ringer[2] in the author's laboratory that dogs lose consciousness when their hemoglobin becomes half saturated with carbon monoxid gas. Ringer's dogs, however, were not beyond the power of resuscitation until 70 per cent. of the hemoglobin was combined with the poisonous gas.

This observation is similar to that of Bornstein and Müller,[3] who have shown that death occurs when 70 per cent. of the hemoglobin of the blood is converted into methemoglobin by magnesium chlorid. Rapid recovery takes place if the process is not carried so far as this.

New and striking experiments by Rosendahl[4] in Kronecker's laboratory indicate that if the atmospheric pressure be reduced

[1] Loewy and Zuntz: "Archiv für Physiologie," 1904, p. 214.

[2] Ringer: Unpublished.

[3] Bornstein and Müller: "Archiv für Physiologie," 1907, p. 470.

[4] Rosendahl: "Zeitschrift für Biologie," 1908, Bd. lii, p. 16.

to such an extent as to produce respiratory distress in rats and rabbits, and then pure nitrogen gas be admitted, the symptoms of suffocation disappear. From this he concludes that diminished atmospheric pressure disturbs the mechanics of blood circulation through the lungs, and that dyspnea in rarefied air is not primarily caused by lack of oxygen in the atmosphere.

Tolerance for the highest altitudes depends on individual idiosyncrasy, which has been variously attributed to differences in the capacity of hemoglobin to absorb oxygen, to differences of diffusion power in the alveolar membrane, and to susceptibility to cosmic influences, such as electric and magnetic phenomena. Or it may be due to the ability of the organism to react so that acid products accumulate which sensitize the respiratory center as Ward's experiments suggest.

The discovery of Viault[1] that at an altitude of 4000 meters the number of red blood-cells increased to 7,000,000 and 8,000,000 per cubic mm. of blood appeared at first to indicate a compensatory increase in oxygen-combining power during life in rarefied air. However, Abderhalden[2] has shown that this phenomenon is due to an expression of blood fluid from the circulatory system and a consequent thickening of the blood, for he finds no change in the total quantity of hemoglobin in animals of the same species when they are killed at different heights. Only after prolonged residence at a high altitude may any increase in the quantity of hemoglobin be possible.[3] Such an increase has been positively shown by Zuntz and his coworkers.[4]

The results of these varied experiments confirm the independence of the metabolism of variations in atmospheric pressure as regards all the customary habitats of mankind. The

[1] Viault: "Comptes rendus de l'academie des sciences," 1890, T. cxi, p. 917.

[2] Abderhalden: "Zeitschrift für Biologie," 1902, Bd. xliii, p. 443.

[3] Abderhalden: "Pflüger's Archiv," 1905, Bd. cx, p. 98.

[4] Zuntz, Loewy, Müller, and Caspari: "Höhenklima und Bergwanderungen in ihrer Wirkung auf den Menschen," Berlin, 1906.

beneficial properties of mountain air may be largely the same as those derived at watering-places, *i. e.*, outdoor life, cool air, exercise, diversion through change of scene, mental rest, and, finally, suggestion of benefits received. The dry, crisp air undoubtedly benefits catarrhal disturbances, which are, on the other hand, aggravated by the climate of the sea-shore.

In the search for conditions which might reduce the intensity of metabolism, the influence of the internal secretions of the sexual glands has been prominently considered. Careful experiments of Lüthje,[1] however, show that castration in dogs of both sexes has no influence on the metabolism. It is said, however, that removal of the ovaries reduces for a time the number of red blood-corpuscles, and it is suggested that ovarian insufficiency may be the cause of chlorosis.[2]

Von Bergmann[3] has shown that although many cases of normal metabolism in obesity have been recorded (see p. 170), he has been able to establish the fact that in some cases there is a constitutional reduction in the intensity of the metabolic processes. Thus he found at certain times in two obese individuals a normal metabolism, which was measured by a heat production of 2100 and 2300 calories and by an excretion of respiratory carbon equal to 180 and 190 grams daily. At other times in these same individuals the metabolism was found to have reached the low values of 1500 and 1780 calories (695 to 662 calories per square meter of surface), while the expired carbon measured 124 and 138 grams. These are the first experiments which establish the existence of a true reduction in the metabolism of obese individuals. The predisposition to obesity may be due to deficient thyroid secretion.

[1] Lüthje: "Archiv für ex. Path. und Pharm.," 1902, Bd. xlviii, p. 184

[2] Breuer and v. Seiller: "Arch. f. ex. Path. und Pharm.," 1903, Bd. l, p. 169.

[3] Von Bergmann: "Zeitschift für ex. Path. und Therapie," 1909, Bd. v, p. 646.

The thyroid gland is a gland whose internal secretion profoundly affects the amount of general metabolism. This influence is apparently brought about by a substance called thyroidin, which, when produced in normal quantities, maintains the proper functions of the nervous system. A subnormal production reduces the activity of the nervous system and incidentally the quantity of metabolism. An over-production increases the irritability of the nervous apparatus and raises the metabolism. Myxedema is a condition in which the thyroid gland has atrophied and its secretion is no longer available. Exophthalmic goiter presents the opposite phase, since here a superabundance of thyroidin is believed to be produced. Symptoms somewhat akin to the latter condition may be induced by ingesting thyroid extracts in normal animals and man.

Magnus-Levy[1] found the carbon dioxid output increased after giving a normal man thyroid extracts. Fritz Voit[2] finds the same to be true of a dog, and also that more protein is metabolized. It is this latter action which contraindicates thyroid feeding in obesity. However, Rheinboldt[3] states that a man fed with thyroid extracts may be maintained in nitrogen equilibrium if much protein be allowed in the diet.

Anderson and Bergman[4] have given large quantities of thyroid extract to a man who was kept in perfect quiet, and no increased output of carbonic acid was noticed. They attribute the increased metabolism which is usually observed to the increased muscle tonus caused by the highly irritated central nervous system. A high metabolism is observed in cases of exophthalmic goiter. Freidrich Müller[5] reports a case of an individual weighing only 29 kilograms who constantly lost weight notwithstanding a daily diet containing 68 grams of

[1] Magnus-Levy: "Berliner klinische Wochenschrift," 1895, Bd. xxx, p. 650.

[2] Voit, F.: "Zeitschrift für Biologie," 1897, Bd. xxxv, p. 116.

[3] Rheinboldt: "Zeitschrift für klin. Med.," 1906, Bd. lviii, p. 425.

[4] Anderson and Bergman: "Skan. Archiv für Physiologie," 1898, Bd. viii, p. 326.

[5] Müller: "Deutsches Archiv für klin. Medizin.," Bd. li, p. 361.

protein with 58 calories per kilogram. Under such circumstances there is undoubtedly an abnormally high destruction of both protein and fat. The increased protein destruction has been attributed to toxic influence of the thyroid secretion. It may, however, be caused by an overheating of the muscle cells due to great heat production. Magnus-Levy[1] finds an increased oxygen intake in cases of exophthalmic goiter amounting to 22, 42, and 70 per cent. above the normal.

Steyrer[2] has made the first complete experiments on the metabolism in this disease. The patient was twenty-one years old, temperature normal; the total metabolism during two days was determined twice at intervals one month apart and while the person was resting in bed. During the second period the disease had made considerable progress, the patient having a hot skin and being in a highly nervous state.

	Day.	Calories of Metabolism.	Weight in Kg.	Calories per Kg.
Period I	1	2665	45.1	59.1
	2	2731	46.4	58.9
Period II (one month later)	1	3666	48.2	76.1
	2	3318	47.5	69.9

In myxedema the metabolism is reduced and there is a fall in body temperature. Anderson[3] reports a case of a woman whose metabolism was as low as 1260 calories or 18.8 per kilogram: after treatment for nine months with thyroid extracets the hat production rose to 2099 calories, or 32.3 per kilogram. These latter are normal values. The temperature rose with the increase in metabolism.

It is possible to explain the reduced temperature as due to disturbances in the nerve mechanism of temperature regulation.

[1] Magnus-Levy: von Noorden's "Handbuch der Pathologie des Stoffwechsels," 1907, p. 325.

[2] Steyrer: "Zeitschrift f. exp. Path. und Therapie," 1907, Bd. iv, p. 720.

[3] Anderson: "Hygeia," Stockholm, 1898 (quoted in Tigerstedt's "Lehrbuch der Physiologie").

The diminished temperature of the body would then be an influence in reducing the metabolism of the cells. This disease is a rare example of a condition in which the metabolic processes are permanently depressed.

Clonic convulsions are a symptom following parathyroidectomy, and during these periods the temperature rises. MacCallum[1] reports that the temperature of a dog in which after parathyroidectomy violent tetany developed, rose from 39° to 43.2° during the attack. The administration of calcium acetate stopped the convulsions in a few minutes and within half an hour the temperature fell to 38.9°.

[1] MacCallum: Fever, Harvey Society Lecture, "Archives of Internal Medicine," 1908, vol. ii, p. 572.

CHAPTER XII.

METABOLISM IN DIABETES AND IN PHOSPHORUS-POISONING.

It is said that the sweet taste of diabetic urine was familiar to Susruta, a physician who lived in India during the seventh century. The disease, then as now, may have been more prevalent among the Hindoos than elsewhere in the world. In Europe the sweet taste of diabetic urine was discovered by Thomas Willis in 1674, but it was not till after another hundred years that Dobson, in 1775, showed that the taste was due to the presence of sugar. Subsequently the coexistence of a hyperglycemia was established.

Claude Bernard found that the stimulation by puncture of a group of cells (the "diabetic center") lying in the medulla near the floor of the fourth ventricle, gave rise to an excretion of sugar in the urine. This experiment is the source of the false impression that diabetes is essentially of nervous origin. It is called *la piqûre*.

Diabetes is a disease of particular interest, since it is a departure from the physiological condition involving the capacity of the organism to care for sugar in the normal fashion. All the symptoms are due to this one fact. No other disease has been more thoroughly investigated. The study of diabetes has wonderfully developed a knowledge of the intermediary metabolism of protein, fat, and carbohydrates. In presenting the details to the reader, it may be remarked that the work done is prophetic of possible accomplishment along scientific lines in the study of disease. It is typical of that "scientific medicine" which affrights the spirits devoted to a passing empiricism.

The foundation of modern knowledge on this subject was

laid by von Mering and Minkowski[1] and by Minkowski[2] alone, who extirpated the pancreas in dogs and demonstrated that such animals became diabetic.

The causes of the appearance of sugar in the urine are: (1) Either the organism cannot burn sugar, which therefore accumulates in the blood in excess of the normal, and is filtered through the kidney (diabetes mellitus, experimental pancreas diabetes); or (2) some tissues may lose their sugar-retaining function so that the normal regulatory control of the quantity of blood-sugar is lost or diminished (Bernard's piqûre, alimentary glycosuria, phlorhizin glycosuria).

The stimulation of Bernard's "diabetic center" is effective in its results only when the liver contains glycogen.[3] This form of glycosuria cannot be obtained in a starving animal. It is attributed to a sudden flushing of the liver with blood and a conversion of glycogen into sugar, so that hyperglycemia and sugar elimination through the kidney follow.

Alimentary glycosuria is seen in normal animals and in man, when sugar is given in larger quantities than the glycogen regulatory function can care for. Moritz[4] found two grams of dextrose in the urine of a man after the ingestion of 200 grams. Such an alimentary glycosuria lasts between three and six hours.

Hofmeister[5] has discovered that the fasting organism is more susceptible to alimentary glycosuria than the well-fed one. He calls such a condition "starvation diabetes." Evidently an organism whose glycogenic function has not been used is less capable of protecting itself from an excess of dextrose than it is during normal nutrition.

Moritz[6] observed 0.2 to 0.3 per cent. of sugar in the urine of

[1] Von Mering and Minkowski: "Archiv für ex. Path. und Pharm.," 1889, Bd. xxvi, p. 371.

[2] Minkowski: *Ibid.*, 1893, Bd. xxxi, p. 85.

[3] Dock: "Pflüger's Archiv," 1872, Bd. v, p. 571.

[4] Moritz: "Verhandlungen des 10 Congresses für innere Medizin," 1891, p. 492.

[5] Hofmeister: "Archiv für ex. Path. und Pharm.," 1890, Bd. xxvi, p. 355.

[6] Moritz: "Archiv für klinische Medizin," 1890, Bd. xlvi, p. 217.

four out of six healthy people who had partaken of a quantity of sweets and champagne.

Evidently such conditions as these are not to be classed with diabetes mellitus, where there is a fundamental disturbance in the sugar-burning power in the organism. It would be of service to distinguish between *glycosurias* where the *sugar-holding* capacity of the organs has been diminished or overstrained, and *diabetes* in which the *sugar-burning* capacity has been affected.

A special type of glycosuria is caused by phlorhizin injections, as was discovered by von Mering.[1] Here the blood itself while passing through the kidney loses the power of retaining its normal sugar content and a hypoglycemia results. Sometimes when the kidney is altered in Bright's disease, phlorhizin is ineffective and no glycosuria follows its administration. The renal character of phlorhizin glycosuria was demonstrated by Zuntz,[2] who placed cannulæ in the upper portions of the two kidneys and injected phlorhizin into the renal artery of one. On the injected side, sugar-containing urine appeared in two minutes, and three minutes later the kidney on the opposite side yielded sugar through its ureter. The delay was due to the lapse of time necessary for the transportation of the phlorhizin by the blood stream from the injected kidney to the other one. In this form of glycosuria sugar ingested *per os*, or subcutaneously, or as formed in protein metabolism, is all eliminated in the urine, provided the quantity given does not flood the organism with sugar.[3] In this latter case part of it can be burned.

Loewi[4] has conceived the idea that the blood sugar is normally in a loose combination with colloid substance. This colloid-sugar cannot pass through the glomerulus. If, however, sugar accumulates in the blood above the combining power of the colloid, then the crystalloid dextrose readily passes away

[1] Von Mering: "Verhandlungen des 5 Congresses für innere Medizin," 1886, p. 185.

[2] Zuntz: "Archiv für Physiologie," 1895, p. 570.

[3] Stiles and Lusk: "American Journal of Physiology," 1903, vol. x, p. 67.

[4] Loewi: "Archiv für ex. Path. und Pharm.," 1902, Bd. xlviii, p. 410.

through the kidney. This condition exists in diabetes mellitus. In phlorhizin glycosuria the kidneys break up the colloid sugar, and the sugar may then be eliminated. Stiles and Lusk, while accepting Loewi's theory, have added the hypothesis that the colloid sugar cannot be burned. Phlorhizin acting in the kidney will split the compound and permit the elimination of sugar. Any free dextrose in the general circulation unites with the colloid radical and is protected from combustion, as is the case when five grams of dextrose are administered subcutaneously, only to reappear in the urine (Stiles and Lusk). If the quantity of sugar in the blood rises above this combining power, immunity from destruction is lost and the sugar burns. The presence of a colloid-dextrose combination is denied by Rosenfeld and Asher,[1] who find that the sugar of normal blood is readily diffusible.

Phlorhizin glycosuria is only temporary in character, and subcutaneous injections of alkaline solutions of the drug three or four times daily are necessary in order to obtain constant results. The character of phlorhizin glycosuria has been dwelt upon because the total metabolism is here identical with that observed in diabetes mellitus.

Von Mering and Minkowski[2] removed the pancreas from dogs and obtained a condition which was markedly analogous to diabetes mellitus in man. There is hyperglycemia and a large excretion of dextrose in the urine; ingested dextrose can not be burned, but is completely eliminated. The dogs show a considerable acidosis, with excretion of β-oxybutyric acid, and they die in coma.[3] If a portion of the gland remain in the abdominal cavity there is either no diabetes or only a partial diabetes. If a portion of a pancreas be transplanted into the abdominal cavity of a depancreatized dog, the diabetes is stopped or reduced as long as the transplanted piece remains functional.

[1] Rosenfeld and Asher: "Zentralblatt für Physiologie," 1905, Bd. xix, p. 449.

[2] Von Mering and Minkowski: "Arch. f. exper. Path. u. Pharmakol.," 1889, Bd. xxvi, p. 371.

[3] Allard: "Arch. f. exper. Path. und Pharmakol.," 1908, Bd. lix, p. 391.

Such experiments as have been made in man have not been successful. Minkowski[1] reports that if a piece of the pancreas be ingrafted under the skin of a dog and afterward the whole of the remainder of the pancreas be removed from the abdomen, the dog's urine remains free from sugar for two months, but on extirpation of the piece ingrafted under the skin an extreme diabetes sets in.

It has long been known that diabetics eliminate sugar even after all administration of sugar is stopped. It has also been generally recognized that protein ingestion tends to increase the sugar output in the urine, while fat has no effect.

A large amount of information has been collected concerning the relation between the urinary nitrogen and sugar elimination in the fasting and meat-fed diabetic organism. The dextrose to nitrogen ratio (D : N) is a key to the problem of the quantity of sugar which can be derived from protein metabolism (p. 132).

Minkowski[2] was the pioneer who discovered that depancreatized dogs, whether fasting or fed with meat, showed a constant elimination of 2.8 grams of dextrose for each gram of nitrogen in the urine. This ratio (D : N :: 2.8 : 1) was the average obtained from seven dogs on twenty-two different days. The lowest ratio was 2.62 : 1, the highest 3.05 : 1. Some other operators have been unable to obtain these ratios. Pflüger[3] finds a variable and generally lower ratio, and his dogs all died of abscesses. Embden's[4] ratios are all lower than Minkowski's, and are probably due to incomplete extirpation of the pancreas.

The accuracy of Minkowski's results is indicated by the fact that the ratio (D : N : : 2.8 : 1) may be easily established by the administration of phlorhizin to rabbits, goats, cats, and in certain dogs whose kidneys have been somewhat affected, as, for

[1] Minkowski: "Arch. f. exper. Path. u. Pharmakol.," 1908, Supplementband, p. 399.

[2] Minkowski: "Archiv für ex. Path. und Pharm.," 1893, Bd. xxxi, pp. 85, 97.

[3] Pflüger: "Das Glycogen," 1905, p. 491.

[4] Embden and Salomon: "Hofmeister's Beiträge," 1904, Bd. vi, p. 63.

example, by giving camphor. Phlorhizin acts first to cause a sweeping out of the excess of sugar in the organism, with a subsequent establishment of the ratio. (See table, p. 285.) The ratios in different animals are given in the following table:

RATIOS IN DIABETES OF D : N : : 2.8 : 1.

Day.	Dog.[1]	Dog.[2]	Cat.[3]	Goat.[4]	Rabbit.[5]
	Pancreas Diabetes.	Phlorhizin and Camphor.	Phlorhizin.	Phlorhizin.	Phlorhizin.
Second day of Diabetes	..	..	..	2.95	2.89
Third " "	2.88	..	2.93	2.90	2.69
Fourth " "	2.94	..	2.80	2.78	..
Fifth " "	3.09	..	2.93	..	..
Day unknown.....	..	2.8	..	..	..

The uniformity of the ratio as shown in different animals is very striking. One may calculate from these results that 45 per cent. of the protein molecule may be converted into dextrose in the course of metabolism.

This, however, does not complete the story of the D : N ratio, for a higher ratio, or 3.75 : 1, was discovered by Reilly, Nolan, and Lusk[6] in the urine of dogs with normal kidneys, after subcutaneous injections of phlorhizin. This ratio was subsequently revised by Stiles and Lusk[7] and found to be 3.65 : 1. The importance of this discovery was enhanced by the finding of Mandel and Lusk[8] that the same ratio may exist

[1] Minkowski: *Loc. cit.*, p. 97.

[2] Jackson: "American Journal of Physiology," 1902, vol. viii, p. xxxii.

[3] Arteaga: *Ibid.*, 1901, vol. vi, p. 175.

[4] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 43.

[5] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1895, vol. i, p. 396.

[6] Reilly, Nolan, and Lusk: *Loc. cit.*

[7] Stiles and Lusk: "American Journal of Physiology," 1903, vol. x, p. 67.

[8] Mandel and Lusk: "Deutsches Archiv für klin. Medizin," 1904, Bd. lxxxi, p. 479.

in human diabetes when the patient is given a diet of meat and fat. These ratios are thus comparable:

Phlorhizinized Dog.[1]	Diabetes Mellitus in Man.[2]
3.60	3.60
3.65	3.65
3.66	3.66
3.62	

A remarkable discovery is that of Falta,[3] who shows that a D : N ratio of 3.6 : 1 may exist in dogs after removal of three of the parathyroids and the pancreas.

In another place (p. 131) it has been shown that the D : N ratio does not vary after the ingestion of sufficient meat to double the quantity of nitrogen in the urine; the sugar also doubles. The sugar production is therefore proportional to the protein metabolism, and, apparently, must be derived from protein.

Various objections have been raised to this statement. Other experiments, however, confirm the above proposition.

Lüthje[4] gave nutrose to a depancreatized dog. Nutrose contains casein but no sugar. The dog weighed 5.8 kilograms and eliminated 1176 grams of glucose during twenty-five days. The tissues of the dog could not possibly have contained over 232 grams of glycogen at the beginning of the experiment. The source of the sugar could not have been the animal's store of glycogen, but must have arisen from either protein or fat.

Pflüger[5] would have it that fat metabolism is the principal source of sugar in diabetes.

The simplest substance from which sugar may be constructed is formaldehyde. Long ago, Baeyer suggested that the formation of sugar in the leaf was through a condensation of formaldehyde molecules into dextrose and Grube[6] has shown that form-

[1] Stiles and Lusk: *Loc. cit.*, p. 77. (Details, this book, p. 70.)

[2] Mandel and Lusk: *Loc. cit.*, p. 479.

[3] Eppinger, Falta, and Rudinger: "Zeitschrift für klinische Medizin," 1909, Bd. lxvii, p. 392.

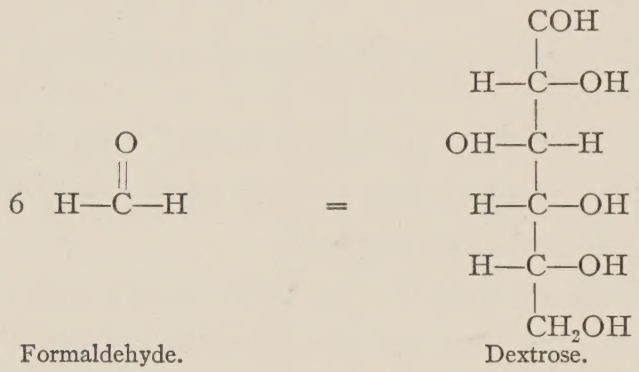
[4] Lüthje: "Pflüger's Archiv," 1904, Bd. cvi, p. 160.

[5] Pflüger: *Ibid.*, 1905, Bd. cviii, p. 115.

[6] Grube: "Arch. f. d. ges. Physiol.," 1908, Bd. cxxi, p. 636.

aldehyde perfused through the liver of a tortoise is converted into glycogen.

The changes described are according to the following formula:



Formaldehyde. Dextrose.

It has already been shown that protein breaks up into amino-acids in the intestines, and that such amino-acids when ingested are the equivalent in metabolism of protein itself (p. 113). Are such amino-acids convertible into dextrose?

Knopf[1] has shown that asparagin given to a diabetic dog yields at least 1.3 grams of dextrose for each gram of its nitrogen metabolized. Stiles and Lusk[2] find that a pancreatic digest of meat, consisting of amino-acids, when given to a phlorhizinized dog, yields 2.4 grams of dextrose for each gram of nitrogen. Embden and Salomon[3] find that glycocoll, alanin and asparagin increase the dextrose output in a diabetic dog.

Pflüger[4] explains that the amino-acids stimulate the fat metabolism in the liver in such a manner as to insure a production of dextrose from fat. This can hardly be correct, for it would be a most remarkable arrangement if amino-bodies carried to the liver of a starving cat under the influence of phlorhizin, and the same quantity carried to the same locality in a dog with pancreas diabetes, should in both cases stimulate exactly the same sugar production from fat.

[1] Knopf: "Archiv für ex. Path. und Pharm.," 1903, Bd. xlix, p. 123.

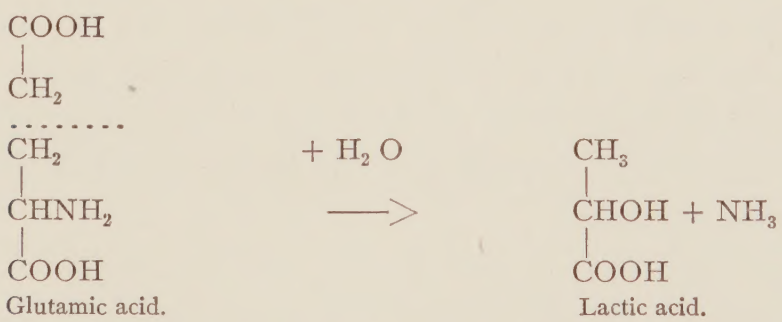
[2] Stiles and Lusk: "American Journal of Physiology," 1903, vol. ix, p. 380.

[3] Embden and Salomon: "Hofmeister's Beiträge," 1904, Bd. v, p. 507; 1904, Bd. vi, p. 63.

[4] Pflüger: *Loc. cit.*, p. 187.

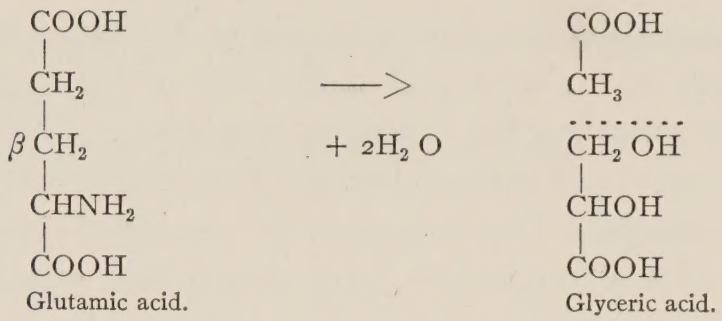
The true situation was first appreciated by Neuberg,[1] who found glycogen in the liver and lactic acid in the urine of a normal rabbit following the ingestion of alanin. The amino-acid alanin is converted into lactic acid by hydrolysis with elimination of ammonia. The ammonia is converted into urea. Arthur Mandel and the writer[2] have shown that d-lactic acid is completely converted into dextrose in the organism, and recently Ringer and the writer[3] have given 20 gm. of i-alanin to a diabetic dog and witnessed its complete elimination in the form of urinary sugar.

In other experiments the writer[4] showed the probability that glutamic acid was convertible into sugar in so far as it could form alanin in the organism. This would take place according to the following reaction, the lactic acid being converted into dextrose:



Or it may be that the cleavage of the glutamic acid may be brought about by hydrolysis of the β-carbon with the production of glyceric acid as follows:

[1] Neuberg and Langstein: "Arch. f. Physiol.," 1903, Supplementband, p. 514.
[2] Mandel and Lusk: "Am. Jour. Physiol.," 1906, vol. xvi, p. 129.
[3] Unpublished.
[4] Lusk: "Am. Jour. Physiol.," 1908, vol. xxii, p. 174.



The glyceric acid would then be converted into dextrose.

A substance like glycocoll might be converted into glycollic acid, and this reduced to glycolaldehyde, a body whose subcutaneous injection leads to an output of sugar in rabbit's urine.[1] These reactions might be as follows:

$$\underset{\text{Glycocoll.}}{CH_2\,HN_2\,COOH} + H_2O = \underset{\text{Glycollic acid.}}{CH_2\,OH\,COOH} + NH_3$$

$$3\underset{\text{Glycolaldehyde.}}{CH_2\,OHCOH} = \underset{\text{Dextrose.}}{C_6H_{12}O_6}$$

It seems probable that the course of the intermediary metabolism involving sugar production is as has been outlined above, and to this list of sugar-producers may be added aspartic acid and probably serin.

Giving fat with meat to a diabetic will not ordinarily increase the sugar in the urine. The writer has never observed such an increase in any of the work of his laboratory. A large production of sugar from fat has been elsewhere reported[2] and Cremer[3] finds that glycerin given alone will increase the output of sugar in the urine.

On giving meat in diabetes the fat metabolism is reduced as it would be in the normal organism, and yet there is no effect on the D : N ratio, and therefore the latter cannot be influenced by the *quantity* of fat burned. This is shown in a respiration experiment made by Mandel and Lusk[4] on a dog

[1] Mayer: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxviii, p. 151.

[2] Hartogh and Schumm: "Archiv für ex. Path. und Pharm.," 1900, Bd. xlv, p. 11.

[3] Cremer: "Münchener med. Wochenschrift," 1902, Bd. xxii, p. 944.

[4] Mandel and Lusk: "American Journal of Physiology," 1903, vol. x, p. 54.

with phlorhizin glycosuria whose metabolism starving and after meat ingestion was as follows:

	D:N.	Calories from Protein.	Calories from Fat.	Calories, Total.
Fasting	3.69	80.2	274.4	354.6
300 grams meat	3.55	161.9	261.7	423.6

The protein metabolism doubled when meat was ingested, the fat metabolism fell, but the D : N ratio remained constant.

It has also been demonstrated that neither exposure to cold nor mechanical exercise, both of which result in a largely increased metabolism of fat, has any effect on the sugar output in pancreas diabetes,[1] or in phlorhizin glycosuria.[2] Thus the writer found in a phlorhizinized dog which had been rid of glycogen by shivering and exercise, that the composition of the urine was unchanged as the result of travelling 1500 meters in a revolving wheel, an effort which would have more than doubled the metabolism of fat during the hour when the exercise was taken. The analytical data for two-hour periods were the following:

	Dextrose.	Nitrogen.	D:N.
Rest	4.57	1.26	3.63
Work, 1500 meters during 1st hour	4.62	1.26	3.67

In this experiment exercise was without influence on the excretion of nitrogen. If, however, the animal contains residues of glycogen which as a result of exercise are converted into sugar and eliminated, then there is also an increased nitrogen elimination as the result of work. This is suggestive of a chemical union between glycogen and nitrogenous substances which may be similar in nature to that of the hypothetical amino-sugars of Lüthje and of Murlin (see p. 123).

If a production of dextrose from fat metabolism be possible, it must be due to a *qualitative* alteration in the metabolism in

[1] Allard: "Archiv für exper. Path. und Pharm.," 1908, Bd. lix, p. 111; Seo, *Ibid.*, p. 341.

[2] Lusk: "American Journal of Physiology," 1908, vol. xxii, p. 163.

rare and special cases. A high authority, von Noorden,[1] writes: "In all *probability* we may even now make the statement that there are a few cases of diabetes in which more sugar is excreted than can be accounted for by the amount of carbohydrate available, and the maximum quantity of protein that could have been disintegrated, and that in these cases fat must be looked upon as the source of the excess."

The theory of the origin of sugar from fat is supported by Falta,[2] who finds a largely increased sugar output after administering adrenalin to dogs with pancreas diabetes. Among the cases of high D : N ratios in human diabetes reported from von Noorden's clinic that described by Bernstein, Bolaffio and Westenrijk[3] is the most remarkable. The ratio, after deducting the carbohydrates ingested in the food, often reached D : N : : 10 : 1. The ammonia nitrogen ran as high as 86% of the total nitrogen, β-oxybutyric acid reached sixty grams per day, and nitrogen equilibrium was maintained on a diet containing only 10.6 grams of nitrogen. Such figures reveal a most exceptional type of diabetes mellitus. The high ratios in diabetes are explained by Falta as being due to very great activity on the part of the adrenals which not only inhibits the internal secretion of the pancreas, but also causes a production of sugar from fat. However, Ringer, working in the author's laboratory, finds that if adrenalin be administered to a fasting phlorhizinized dog, although the first administration of the drug may bring about an elimination of "extra sugar" which may be discharged from the glycogen repositories of the body on account of the anemia of the tissues (see p. 255), a second injection of adrenalin may be entirely without influence on either the sugar or nitrogen elimination. This indicates that adrenalin does not cause a production of sugar from fat.

[1] Von Noorden: "Diabetes," Herter Lectures, 1905, p. 80.

[2] Eppinger, Falta and Rudinger: "Zeitschrift für klinische Medizin," 1908, Bd. lxvi, p. 1.

[3] Bernstein, Bolaffio, and Westenrijk: "Zeitschrift für klinische Medizin," 1908, Bd. lxvi, p. 1.

Falta explains the results of many experiments by stating that while the secretory activities of both thyroid and adrenals are each stimulated by the secretions of the other, the activity of the pancreas is in like manner inhibited by the secretions of the other two glands. Therefore supersecretion of adrenalin inhibits the secretory function of the pancreas so that the organism can no longer oxidize carbohydrates and at the same time it stimulates the thyroid, causing increased protein metabolism. Furthermore in exophthalmic goiter, where there is supersecretion in the thyroid gland, there is a tendency to glycosuria, and it is believed that true diabetes has been induced by this cause.[1] Administration of thyroid extracts to dogs also produces glycosuria. Cecil,[2] working under Opie's direction, finds lesions of the pancreas in cases of diabetes associated with exophthalmic goiter. It has already been noted that the extirpation of the parathyroids in depancreatized dogs raises the urinary D : N ratio from 2.8 to 3.65, which shows that these glands are in some way related in their influence over carbohydrate metabolism.

A question of special interest is the cause of the two D : N ratios, 2.8 : 1 and 3.65 : 1. The former represents a production of 45 per cent., the latter one of 58 per cent. of sugar from meat protein. In neither case can ingested dextrose be burned. It is, of course, possible that the sugar production varies under different circumstances; that is to say, the organism (liver?) may be able at times to produce sugar from a certain class of protein decomposition products, and at other times not. For example, it has been noted (p. 279) that glutamic acid is convertible into dextrose in the dog, but Neuberg[3] testifies that it may also be converted into butyric acid from which sugar cannot be formed. Or, one may adopt the hypothesis of Mandel and Lusk,[4] which

[1] Magnus-Levy: von Noorden's "Handbuch des Stoffwechsels," 1907, Bd. ii, p. 333.

[2] Cecil: "Journal of Experimental Medicine," 1909, vol. xi, p. 266.

[3] Brasch and Neuberg: "Biochemische Zeitschrift," 1908, Bd. xiii, p. 299.

[4] Mandel and Lusk: "Deutsches Archiv für klinische Medizin," 1904, Bd. lxxxi, p. 491.

assumes a difference between α-colloid dextrose and β-colloid dextrose existing in the blood. By α-dextrose is understood the amount of dextrose represented by the ratio D : N : : 2.8 : 1, or 45 per cent. of the protein. The β-dextrose represents the additional 13.6 per cent. of the protein, when the ratio 3.65 : 1 is present. The ratio would depend on the combustion or non-combustion of the β-dextrose. If the latter burns, it must do so as a complex, for as free dextrose it would be eliminated in the urine.

This theory of a difference in chemical union would explain the fact discovered by Straub[1] for carbon monoxid "diabetes" and by Seelig[2] for glycosuria following ether inhalation, that sugar appears in the urine in large quantity if a dog be fed with meat, but disappears if the animal be given carbohydrate alone. Seelig found no glycosuria when an intravenous infusion of oxygen was administered at the same time that ether was given. It may be that lack of oxygen causes a dissociation of either α- or β-colloid dextrose derived from protein, which dextrose then appears in the urine. This suggestion is, however, highly speculative.

One of the very pronounced characteristics of the diabetic is his constant emaciation. There is usually a larger excretion of nitrogen in the urine than is necessary for a healthy person. It may be recalled that carbohydrates diminish the protein metabolism, and also that a person may support life on meat and fat alone without tissue waste. But in this latter case there is a supply of carbohydrate derived from protein metabolism. This is also true in starvation. But when the protein sugar is withdrawn from the tissue cells in diabetes, there is at once a largely increased protein metabolism. This is most obvious in fasting animals treated with phlorhizin, as this glycosuria can be immediately induced. The increase in protein metabolism is most marked where the higher D : N ratio exists. In this

[1] Straub: "Archiv für ex. Path. und Pharm.," 1896, Bd. xxxviii, p. 139.

[2] Seelig: *Ibid.*, 1905, Bd. lii, p. 481.

connection the following experiments on fasting animals are suggestive:

TABLE ILLUSTRATING THE INFLUENCE OF DIABETES ON PROTEIN METABOLISM.

	Goat.[1]			Dog.[2]		
	D.	N.	D:N.	D.	N.	D:N.
Fasting.....	.....	3.72	....	.....	4.04	....
Fasting.....	.....	3.71	....	.....	4.17	....
Fasting and diabetic	20.33	4.90	4.15	63.55	12.66	5.02
" "	26.08	8.83	2.95	65.30	18.76	3.38
" "	23.39	8.06	2.90	65.84	18.57	3.54
" "	19.01	6.84	2.78	64.60	17.29	3.74

In the goat the protein metabolism rose to 238, in the dog to 450 per cent. of that in the normal animals, as the result of the loss of the influence of the small quantity of protein sugar produced in starvation.

Falta, Grote, and Staehelin[3] found a rise in the protein metabolism of fasting dogs which had been depancreatised, equal to five-fold the normal amount.

In the case of diabetes mellitus reported by Mandel and Lusk where the ratio D : N was 3.65 : 1, it was found that the ingestion of broths containing 7.7 grams of nitrogen was followed by an elimination of 21.7 grams of nitrogen in the urine or a loss of body nitrogen approximating 14 grams. The patient was greatly emaciated, and passed this day in bed. He could not be maintained in nitrogen equilibrium with 19 grams of protein nitrogen in the food, but was in nitrogen equilibrium when given 27 grams. In all cases of intense diabetes this factor of an increased protein metabolism must be considered. In mild cases in which sugar disappears from the urine when

[1] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 43.

[2] Reilly, Nolan, and Lusk: "American Journal of Physiology," 1895, vol. i, p. 397.

[3] Falta, Grote, and Staehelin: "Hofmeister's Beiträge," 1907, Bd. x, p. 199.

carbohydrates are cut out of the food, and in which the patient may burn his protein sugar, the protein metabolism is not different from that of a normal person living on meat and fat.

Among the earliest investigations of Pettenkofer and Voit[1] was a respiration experiment on a diabetic individual. The authors compared the metabolism of a diabetic with that of a normal man, as is indicated in the following table:

COMPARISON OF A NORMAL AND A DIABETIC MAN.

	Grams in the Food.	Grams Burned in the Body.
Healthy man, Protein	120	120
" " Fat	112	83
" " Sugar	344	344
Diabetic man, Protein	107	158
" " Fat	108	158
" " Sugar	337	0
(337 grams of sugar in the urine.)		

It is seen here that the fat and protein metabolism are increased in order to compensate for the non-combustion of the sugar. Several years later, on the basis of these experiments, E. Voit calculated that a diabetic on a moderate mixed diet yielded 1015 calories per square meter of surface, while the normal individual of similar build produced 1020 calories. Falta,[2] working with Benedict in Boston, finds that the total metabolism of men suffering from severe diabetes is unchanged from the normal.

The diabetic condition, therefore, does not involve a decrease in the quantity of energy produced, but only an alteration in the source of the energy. This fact can be made still more strikingly apparent by comparing the metabolism of a normal fasting dog with the metabolism of the same dog made diabetic with phlorhizin. Such an experiment was first done by the writer[3] on a fasting dog of 11 kilograms and with the following results:

[1] Pettenkofer and Voit: "Zeitschrift für Biologie," 1867, Bd. iii, p. 380.

[2] Falta: "Wiener klin. Wochenscher.," 1909, Bd. xxii, No. 16.

[3] Lusk: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 31.

COMPARISON OF NORMAL AND DIABETIC METABOLISM IN THE SAME FASTING DOG.

	Grams Burned in the Body.	Calories from Metabolism.
Normal, Protein	20.19	80.68
Fat	55.87	526.13
Total		606.81
Diabetic, Protein	67.38	128.08
Fat	51.15	481.69
Total		605.77

(39.4 grams dextrose in urine. D : N :: 3.65 : 1)

It is apparent from the above experiment that the protein metabolism of the diabetic dog increased to 333 per cent. of that of the dog when normal. The fat metabolism slightly decreased, but the total energy derived from the metabolism was exactly the same in both cases.

Rubner[1] has rightly criticized this experiment for neglect to record the temperature at which it was carried out. Rubner has repeated the work when the dog was kept in a room having the temperature of 33°, but the D : N ratio in this dog was only 2.8 : 1 on the second day of diabetes, and Rubner also did not take into account the preliminary clearing out of the body sugar which raised his ratio on the first day. These facts, however, do not invalidate his conclusions.

Rubner finds the metabolism on the fasting days to be the equivalent of 477.8 calories and on the diabetic days to be 510.4, an increase of 32.3 calories per day in diabetes. This increase Rubner attributes to the specific dynamic action of the increased protein metabolism. This increase in protein destruction in the diabetic dog amounted to the equivalent of 101.1 calories. Rubner therefore calculates that through the extra metabolism of the equivalent of 100 calories in protein, 31.9 of extra heat production arises. This agrees with his values elsewhere discussed (p. 160). Rubner's results do not conflict with the writer's experiment, for at a room temperature below 33° the

[1] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 370.

calories of the chemical regulation of temperature are replaceable by those derived from the specific dynamic action of protein, without any alteration in the total of the metabolism.

The specific dynamic action of protein ingested in diabetes is also illustrated in the experiment given on page 281. The knowledge at hand makes it possible to estimate the energy value of protein to the diabetic. It may be calculated from the D : N : : 3.65 : 1 that 52.5 per cent. of the energy in meat protein is lost to the organism in the form of dextrose. Rubner teaches that 28.5 per cent. of the energy of meat protein is never utilized in the service of the life processes of the cell, but is liberated as free heat (p. 163). There remains a balance of only 19 per cent. which is actually available for maintenance of the vital activities in diabetes. The three- to five-fold increase in protein metabolism, however, nearly neutralizes this great waste of energy, and leaves the fat metabolism very much as in the normal organism.

The distribution of the energy from protein in the diabetic, as described above, may thus be summarized:

100 PROTEIN CALORIES.

28.5 for cleavage and deamination.	71.5 for life processes.
Deduct	52.5 energy in dextrose.
	19.0 balance available = x.

The production of dextrose from protein involves the absorption of a good quantity of oxygen. Magnus-Levy,[1] calculating that 60 grams of dextrose arise from those decomposition products of 100 grams of protein which do not appear in the urine and feces (p. 37), gives the following table indicating the requirement for oxygen when protein burns in diabetes:

100 grams protein..... =	38.6 C.	4.24 H.	9.24 O.
60 " dextrose .... =	24.0 C.	4.0 H.	32.0 O.
Balance requiring respiratory O..... +	14.6 C.	+ 0.24 H.	—22.8 O.

[1] Magnus-Levy: "Archiv für Physiologie," 1904, p. 379.

A further calculation showed that the respiratory quotient for protein in this diabetic condition was reduced from the normal of 0.808 to 0.613. Oxygen is not only used to form water and carbon dioxid, but it is also used to form sugar. Hence in severe diabetes the respiratory quotient may fall below that representing fat metabolism.

The preëminence of fat metabolism in the diabetic as the mainstay of his organism leads to inquiry as to the origin of the fatty acid called β-oxybutyric acid, and of aceto-acetic acid and acetone which are directly derived from it.[1] Whence do these acetone bodies arise? They were at first supposed to come from dextrose, following a chemical process analogous to the butyric acid fermentation of carbohydrates, but it was soon discovered that in normal persons the acetone bodies were especially found in the fasting state. Many then attributed the presence of acetone to the specific breakdown of body protein, since, when protein was given in the food, the acetone bodies disappeared in the urine. However, Magnus-Levy[2] has reported a case of a boy in coma who eliminated an average of 97.5 grams of β-oxybutyric acid and aceto-acetic acid daily for three days in addition to an unmeasured quantity of acetone in the breath, and during this time the protein metabolism amounted to 90 grams, of which latter at least 40 grams appeared as sugar in the urine. The 97.5 grams of acetone bodies in this case could not have been entirely derived from the 90 grams of protein, but they must have originated largely from fat.

Stadelman[3] first pointed out the relationship between the formation of β-oxybutyric acid and the occurrence of coma. Coma has been compared to the sword of Damocles which hangs suspended over every diabetic. It has been discovered that whenever the organism is thrown suddenly from a carbohydrate regimen to a combustion of fat the acetone bodies appear

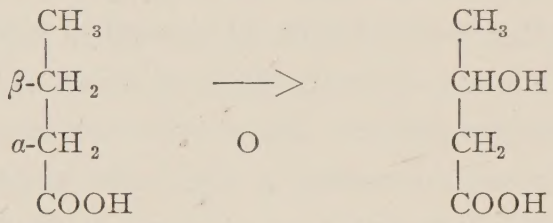
[1] This description is taken from Lusk: Metabolism in Diabetes, Harvey Society Lecture, "Archives of Internal Medicine," 1909, vol. iii, p. 1.

[2] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, Bd. i, p. 374.

[3] Stadelman: "Experimentelle-klinische Untersuchungen," Stuttgart, 1890.

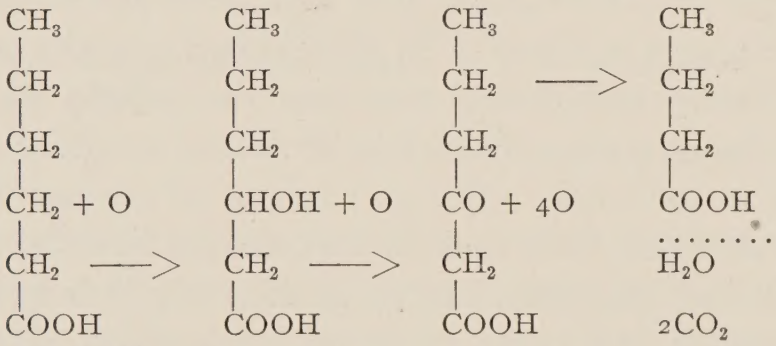
in the urine. This condition is greatly intensified in diabetes when even the sugar derived from protein is not burned.

Knoop,[1] through cleverly devised experiments, has shown that the oxidation of fatty acids in the body is effected by an attack on the fatty molecule at the carbon in the β-position. Thus, the first step in the metabolism of butyric acid would be the oxidation of its β-carbon atom as follows:



Butyric acid. β-oxybutyric acid.

In a similar manner, caproic acid would first be oxidized at its beta-carbon atom and then on further oxidation would lose two atoms of carbon and be converted into butyric acid, which, in turn, becomes β-oxybutyric acid. These reactions may be written as follows:



Caproic acid.

Such, indeed, is believed to be the method of successive oxidation of all the fatty acids, of palmitic acid, $C_{16}H_{32}O_2$, and of stearic acid, $C_{18}H_{36}O_2$. It is evident that each successive oxidation carries away two carbon atoms and that β-oxybutyric acid can be produced only from fatty acids having an even number of carbon atoms. Valerianic acid, for example, with

[1] Knoop: "Beitr. z. chem. Physiol. u. Path.," 1904, Bd. vi, p. 150.

five atoms of carbon, can not yield β-oxybutyric acid. The organism has an apparent preference for fats with an even number of carbon atoms, and each of these fatty acids on its way in metabolism yields a molecule of β-oxybutyric acid.

Each molecule of butyric acid can yield one of β-oxybutyric acid. It has been calculated by Magnus-Levy[1] that 100 grams of neutral fat made of stearin, palmitin, and olein may yield 36.2 grams of β-oxybutyric acid. It is, therefore, evident that the higher fatty acids are the more valuable nutriment. Butter, with its high content of butyric acid, largely increases the output of the acetone bodies in diabetes. Fifty to 100 grams of butter fat when administered to a diabetic may raise his acetone output four to eightfold.[2] Oleomargarin is to be preferred.

Joslin[3] has shown that oleic acid yields acetone more readily in diabetes than do palmitic and stearic acids.

Normal oleic acid has a double band between the two carbon atoms which are in the middle of its chain; in other words it is an unsaturated fatty acid. Such acids on oxidation break up into two, the cleavage taking place at the double link. In the case of oleic acid the following reactions take place:

$$\underset{\text{Oleic acid.}}{C_8H_{17}CH : CHC_7H_{14}COOH} \longrightarrow$$

$$\underset{\text{Pelargonic acid.}}{C_8H_{17}COOH} + \underset{\text{Azelaic acid.}}{COOH\ C_7H_{14}COOH}$$

Leathes[4] has pointed out that the oleic acid found in the liver does not yield these acids, but only caproic acid is found on oxidation. Leathes therefore states that the liver acts on the double linkage causing its transposition on the fatty acid chain to a point where the oxidation becomes more easy. Furthermore Leathes finds that the liver causes the formation of new double bands in fatty acids which reach it, thereby preparing them for readier oxidation. The liver therefore

[1] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, Bd. i, p. 384.

[2] Fejes: "Magyar orvosi Archivum," 1907, Bd. viii, p. 335.

[3] Joslin: "Jour. Med. Research," 1904, Bd. xii, p. 433.

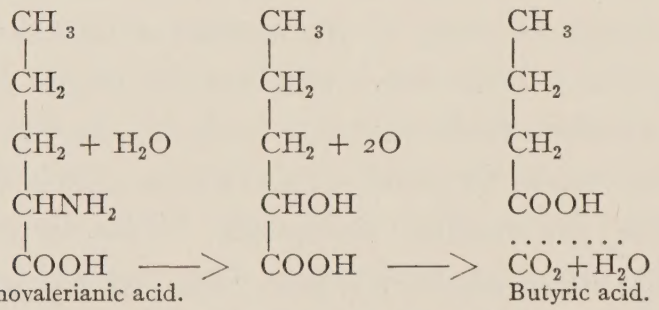
[4] Leathes: Harvey Society Lecture, "Lancet," 1909, vol. clxxvi, p. 593.

desaturates fatty acids and transposes unsaturated linkages, in the interest of the readier oxidation of the fats when they are returned to the tissues to yield energy for the maintenance of life. This explains the filling of the liver with fat when the organism no longer burns carbohydrates. The fat of the subcutaneous layers is transported to the liver to be worked over and is then distributed to the cells of the organism in a form which is more readily available than before.

One can realize from this that the short chains of oxy-acids derived from protein in metabolism are much more available for cellular metabolism than are the ordinary fatty acids, and would be oxidized first.

The story of the formation of β-oxybutyric acid does not end with the metabolism of fat, for many of the amino-acids of protein yield this acid in metabolism. From the experiments of Embden, Salomon and Schmidt,[1] Baer and Blum,[2] it has been discovered that leucin may yield β-oxybutyric acid, whereas amino-butyric and normal amino-caproic acids do not. Friedrich Müller, in his Herter lectures, mentioned the fact that he had administered amino-valerianic acid to a diabetic patient, with resulting increase in the β-oxybutyric acid excretion.

These statements are all conformant with the idea of a β-oxidation of fatty molecules. Thus, when α-amino-valerianic acid is ingested, it undergoes hydrolysis in the intestinal wall and loses ammonia. Its further oxidation results in the production of butyric acid, which is now oxidized at the β-carbon. The reaction is as follows:

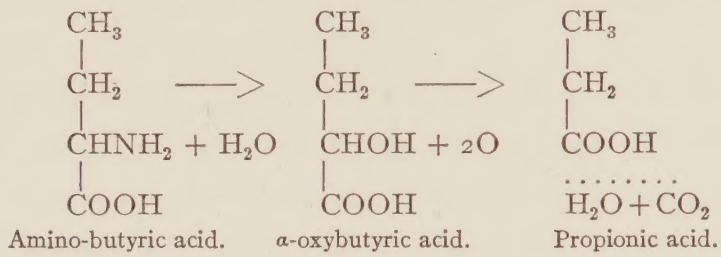


α-Aminovalerianic acid. Butyric acid.

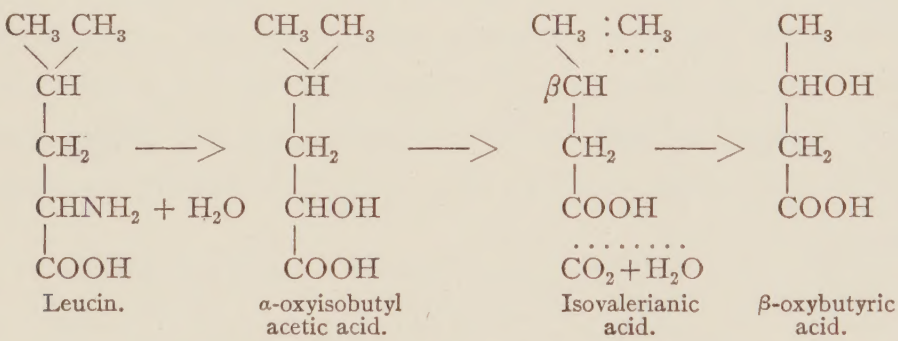
[1] Embden, Salomon and Schmidt: "Beitr. z. chem. Physiol. u. Path.," 1906, Bd. viii, p. 129.

[2] Baer and Blum: "Arch. f. exper. Path. u. Pharmakol.," 1906, Bd. lv, p. 89.

In a similar manner amino-butyric acid and amino-caproic acid would produce, respectively, propionic and valerianic acids, neither of which is convertible into β-oxybutyric.

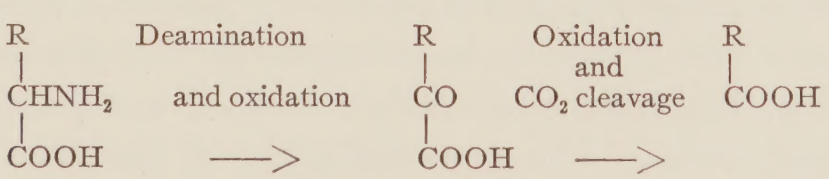


In the case of leucin, iso-valerianic acid would be the intermediary product, and it has been shown that this fatty acid with its broken chain is convertible into β-oxybutyric acid in the organism.



It may also be added that Embden[1] has shown that homogentisic acid and its precursors tyrosin and phenylalanin yield acetone on perfusion through an excised liver. Hence the benzol ring when it is broken in the body yields a normal product of fatty acid oxidation (see p. 136).

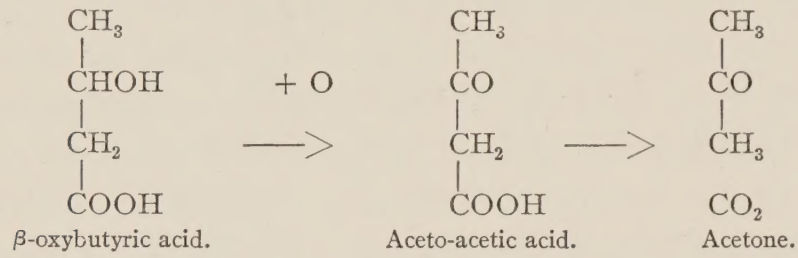
Ketonic acids are also intermediary products here, resulting from the oxidation of the oxy-acids. Neubauer[2] gives the following general scheme for the oxidation of amino-acids:



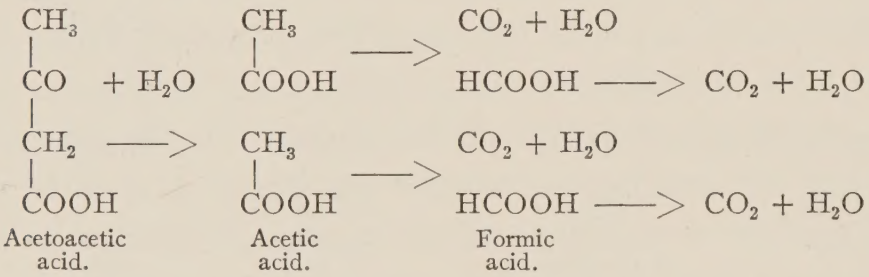
[1] Embden, Salomon, and Schmidt: *Loc. cit.*

[2] Neubauer: "Deutsches Archiv für klinische Medizin," 1909, Bd. xcv, p. 211.

Dakin[1] has shown that peroxid of hydrogen acting on amino-acids converts them into ketonic acids. After a similar fashion acetone arises from β-oxybutyric acid, as follows:



Since acetone is with difficulty oxidized in the body, it is probable that *in the normal process of oxidation* the acetoacetic acid formed is directly converted into two molecules of acetic acid, and these through formic acid into carbon dioxid and water, as follows:



Amino-acids which form sugar on ingestion, such as glycocoll, alanin, aspartic acid and glutamic acid, do not form β-oxybutyric acid, but may rather decrease the quantity produced, especially if the sugar formed can burn. This explains why the acidosis in fasting is reduced on ingestion of meat. Baer and Blum[2] gave 10 grams of alanin to a dog which received about a gram of phlorhizin daily. The sugar output was raised from 19.5 to 21.5 grams. Since we have seen that alanin is completely convertible into dextrose, it follows that much of it must have been burned in the incompletely phlorhizinized dog. Therefore, the acetone excretion decreased and β-oxybutyric acid disappeared. The profound effect of the ingestion of

[1] Dakin: "Journal of Biological Chemistry," 1908, vol. iv, p. 221.

[2] Baer and Blum: "Beitr. z. chem. Physiol. u. Path.," 1907, Bd. x, p. 90.

glutaric acid in reducing sugar and nitrogen output as well as the acetone bodies may find a similar explanation. It is certain that the skilfully planned work of Baer and Blum loses a large part of its significance because of the too small and too infrequent dosage with phlorhizin.

Magnus-Levy[1] gave 11.7 grams of β-oxybutyric acid to a normal dog. This was completely burned. He then gave 11.5 grams to a phlorhizinized dog, with the result that there was an increased elimination of 7.6 grams of β-oxybutyric acid and acetone. Since some acetone was eliminated in the breath, it is evident that the animal had largely lost the power to burn ingested β-oxybutyric acid.

On the basis of work on a diabetic and comatose boy weighing 32 kg., Magnus-Levy[2] makes the following computation of metabolism. He purposely assumes a high requirement of energy for a lad of this size, or 50 to 55 calories per kilogram, which calls for a total of 1600 to 1700 calories. The boy burned 90 grams of protein and perhaps 200 grams of fat:

	Calories.
90 grams protein = 369 calories 200 grams fat = 1,909 calories	= 2278
Deduct 97.5 grams oxybutyric acid, 443 calories Deduct 50 grams urinary sugar, 185 calories ..	= 628
Calories available	1650

Here we perceive an extreme case of diabetic metabolism in which half the energy contained in protein is excreted in urinary sugar and 20 per cent. of that contained in fat is eliminated in the unburned β-oxybutyric acid.

This, then, is the worst picture of the perverted metabolism in diabetes. Sugar can not burn, fat burns only as far as β-oxybutyric acid, and as for protein a part of its amino-acids are converted into sugar and another part into β-oxybutyric acid, neither of which can be burned.

[1] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, Bd. i, p. 372
[2] Magnus-Levy: *Ibid.*, p. 385.

Rosenfeld has said that fat can burn only "in the fire of carbohydrates." But this is not true. Mandel and the writer, in their work on a diabetic with a D : N ratio of 3.65 to 1, and who had no tolerance for carbohydrates, found a low acidosis as measured by a maximum excretion of 2 grams of ammonia, no β-oxybutyric acid, and a maximum of 0.8 gram of acetone per day. On the other hand, von Noorden[1] and Magnus-Levy[2] report cases in which there was a considerable excretion of acetone bodies in the urine when carbohydrates were burned. For example, one patient eliminated 4.9 grams of β-oxybutyric acid on a day when 40 grams of starch were ingested and burned. There are great individual variations. Thus, Stäubli[3] reports concerning a diabetic man whose ordinary mixed diet was changed to one of meat and fat, including 50 grams of bread, the whole containing 3200 calories. After ten days of this diet, during which the sugar output remained nearly constant at 100 grams, the β-oxybutyric acid fell from 37.5 grams daily to nothing. In commenting on his results Stäubli says: "The important factor which causes a more serious condition in the metabolism of a diabetic is the quantity in which carbohydrate is administered in excess of the tolerance for sugar. Damage caused by a continual overworking of the sugar-burning capacity plays a large part in the progress of the disease. The considerable withdrawal of carbohydrates from the diet, even in cases of severe diabetes with high acidosis, exerts an extraordinarily beneficial influence. This can be, in part, explained by the increased ability to burn sugar on account of the conservation of the body's power in this direction. The improvement in the capacity for sugar combustion exerts on its side a beneficial action on the acidosis."

The damage done in severe diabetes by flooding the organism with carbohydrates is illustrated by the fate of a diabetic in-

[1] Von Noorden: "Pathologie des Stoffwechsels," 1907, Bd. ii, p. 77.
[2] Magnus-Levy: "Ergebnisse d. inn. Med.," 1908, Bd. i, p. 404.
[3] Stäubli: "Deutsch. Arch. f. klin. Med.," 1908, Bd. cxiii, p. 125.

dividual who had been kept on a restricted diet at the advice of the writer, but on the recommendation of a consultant was given a large quantity of carbohydrate; this resulted in onset of coma, which proved fatal.

The great individual variations as regards the presence of the acetone bodies seem to warrant the opinion which the writer expressed in a discussion on acidosis at Washington in 1907, that one may assume the existence of a specific β-oxybutyric acid ferment analogous to the ferment which breaks down the sugar. Such a ferment would split β-oxybutyric acid, thereby performing one of the last offices of cleavage of the fatty molecules. Injury to this ferment may be complete or partial even as in the case of the sugar ferment, but damage to one does not necessarily involve proportionate damage to the other.

The elimination of β-oxybutyric acid from the system is furthered by the administration of alkalis. Stäubli reports a diabetic who eliminated 34 grams of β-oxybutyric acid daily when the diet contained 60 grams of sodium bicarbonate. This excretion fell to 17 grams on a diet which was free from alkali, and then rose to 45.2 grams, on return to 60 grams of bicarbonate. Such treatment with alkali is highly beneficial, for, as Magnus-Levy observes, the diabetic does not die in coma because of the neutralized acid which is eliminated in the urine, but rather on account of that which is retained in the body which neutralizes the alkalis of tissue and of body fluids.

Von Noorden[1] reports cases of diabetics who have excreted 5 to 6 grams of acetone and 30 to 40 grams of β-oxybutyric acid in a day, and yet have lived comfortably for years.

Minkowski[2] noted that the livers of his depancreatized dogs were free from glycogen, and this fact has been confirmed by other observers. He also found that when levulose was given, glycogen could be stored. The glycogenic function is inhibited

[1] Von Noorden: Von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 253.

[2] Minkowski: *Loc. cit.*

in so far as glycogen production from dextrose is concerned, but it is not destroyed as regards levulose and galactose. This relation may simply indicate that, perhaps through some property of the liver, glycogen is not formed from dextrose when dextrose is needed for the tissues. The livers of human beings who have died of diabetes contain little or no glycogen, though here the results are not so significant as in dogs, because of hunger and suffering which may precede natural death in this disease.[1]

The present discussion of metabolism in diabetes has been principally directed along lines involving the most intense forms, where the ability to burn sugar is totally absent. It has been observed that there are many intermediary stages in this disease in which the power to burn dextrose is very different. To determine the intensity of diabetes, Von Noorden has prepared a standard test-diet which is largely employed in Germany. This diet is divided into portions for three meals. At breakfast and at lunch fifty grams of bread are allowed. The other nutrients are meat, eggs, bacon, butter, green vegetables, cheese, lettuce salad, coffee, and wine. Should the urine of the diabetic be free from sugar on such a diet, the diabetes is mild in character. More bread may then be added to the diet from time to time and the commencement of sugar excretion in the urine watched. When sugar appears the limit of tolerance for carbohydrate has been reached. If, however, the urine contains sugar on the above test-diet, the quantity of bread is reduced, and the urine may then become free from sugar. If the urine contains sugar after all the bread has been removed from the diet, the case is one of severe diabetes. Even here the sugar may disappear from the urine on reducing the protein in the diet and thereby cutting down one supply of carbohydrate. A diabetic of this order may live on a low protein dietary with

[1] Literature by Magnus-Levy: Oppenheimer's "Handbuch der Biochemie," 1909, Bd. iv, 1, p. 357.

enough fat to furnish sufficient energy for his body's requirement, even as a normal man may exist.

Mandel and Lusk[1] have commended another method for the clinical examination of severe types of diabetes, using the D : N ratio for this purpose. The procedure is as follows: If a diabetic be given a meat-fat diet (rich cream, meat, butter, and eggs) and the twenty-four hour urine of the second day be properly collected,[2] the discovery of 3.65 grams of dextrose to one gram of nitrogen signifies a complete intolerance for carbohydrates and probably a quickly fatal outcome. The authors called this (D : N :: 3.65 : 1) *the fatal ratio.*

A lower ratio of dextrose to nitrogen on this diet indicates that some protein sugar may be burned. Such a tolerance for sugar may be increased on a meat-fat diet so that the D : N ratio falls, and in favorable cases the dextrose may entirely disappear from the urine.

In the case of the medical student of Mandel and Lusk, the ratio was constantly 3.65 : 1 and the progress of the disease rapidly fatal, death occurring six weeks after the ratio was discovered. In another case of the same investigators, a diabetic was revived from coma with sodium bicarbonate; then, after two days, the meat-fat diet was given. On the second day of this diet the D : N ratio was 2.91 : 1; on the tenth day, 0.34 : 1; on the twenty-third day the patient's urine was free from sugar and he was eating a small amount of carbohydrate. This is an illustration of improving tolerance when a diabetic is placed on a diet which is free from carbohydrates. Good practice calls for the occasional interpolation of periods in which the dietary is free from carbohydrates, on account of the beneficent effect on the power of the diabetic to burn sugar.

[1] Mandel and Lusk: "Deutsches Archiv für klinische Medizin," 1904, Bd. lxxxi, p. 472.

[2] The urine should be collected so that an early morning hour (before breakfast) terminates the period for one day. This is necessary because the dextrose arising from ingested protein is eliminated before the nitrogen belonging to the same (p. 130). The long period between the evening meal and breakfast allows for the elimination of both constituents.

The above-mentioned individual appeared to be doing well, two years after the test, but had to look carefully to his dietary. His D : N ratio after one week of a strict meat and fat diet was 2.8 : 1, which indicated a less favorable outlook than two years before. He had not lost in weight and went about his usual occupation. A year later he died in coma.

Physicians will object to this manner of investigation because there is no ready method of determining the nitrogen in the urine. With the growth of laboratories for medical work, this difficulty will be removed. A frequent source of error is the untrustworthiness of the ordinary diabetic patient, who will privately eat carbohydrate in spite of the physician's prohibition.

Having discovered by investigation the tolerance of a diabetic for carbohydrates, the next step is to see that the patient is supplied with a sufficient amount of energy in the food to correspond with the requirement of his organism (35 calories per kilogram). A diabetic with no tolerance for carbohydrates will require between 200 and 250 grams of fat according to his weight. This amount will not be taken unless all the devices of variation in flavor be made use of. The patient will not take it of his own accord, and the amount required should be carefully allotted, preferably in a sanatorium. Diabetics can be educated in such establishments to a proper course of dieting which is the only hope for the amelioration of their troubles. Alcohol may be used, in part, to furnish the necessary calories in the diet. Benedikt and Török[1] were able to reduce the acetone excretion, as well as that of nitrogen and dextrose, after administering alcohol to a diabetic. Stäubli,[2] however, states that alcohol may in some cases reduce the tolerance of the diabetic for carbohydrate.

There is no known cure for diabetes. There is nothing except dieting that affords permanent relief. Opium is said to

[1] Benedikt and Török: "Ztschr. f. klin. Med.," 1906, Bd. lx, p. 329.

[2] Stäubli: "Deutsch. Arch. f. klin. Med.," 1908, Bd. cxiii, p. 125.

reduce the sugar output in cases bordering on the severe type.[1] The cause of this action is unknown. Experiments inaugurated upon an individual having the 3.65 : 1 ratio might indicate whether its effect was really to increase the combustion of sugar or only to reduce the general metabolism. The ingestion of extracts of different organs does not apparently influence the sugar excretion. Laboratory investigations of the glycolytic power of pancreas extracts have been very numerous, but have failed to give striking results. It is possible that the supposed enzyme or activating substance is extremely sensitive to a change in normal conditions. Mandel and Lusk gave large quantities of yeast to a diabetic man without changing the D : N :: 3.65 : 1, which shows that the enzymes of yeast are not able to penetrate the intestinal wall so that they may replace the natural ferment of the organism.

Minkowski[2] discovered that levulose largely reduced protein metabolism in the case of depancreatized dogs. This led to the widespread use of levulose in diabetes. Mandel and Lusk, however, found that the increase of sugar in the urine of their diabetic man, after giving 100 grams of levulose, was 80 per cent. of the sugar ingested. The levulose had no effect whatever on protein metabolism.

Von Noorden[3] confirms this observation. He also states that in severe cases of diabetes, levulose appears in the urine. He believes that levulose is normally produced in metabolism and is normally burned. In very rare cases called levulosuria, levulose alone appears in the urine. One case of complete intolerance for levulose has been reported.[4] Very likely in Minkowski's depancreatized dogs the power of oxidizing levulose was entirely normal.

The negative results as regards the value of levulose were

[1] Von Noorden: "Diabetes," 1905, p. 158.
[2] Minkowski: *Loc. cit.*, p. 131.
[3] Von Noorden: *Loc. cit.*, p. 50.
[4] Neubauer: "Münchener med. Wochenschrift," 1905, p. 1523.

especially interesting in the case of Mandel and Lusk. This diabetic medical student was confident of the efficacy of levulose on account of opinions expressed by the writer in his lectures. On the days of levulose ingestion the patient's spirits revived, his strength, measured on the ergograph, decidedly improved and his companions remarked upon the benefit received. All of which shows that subjective sensations are not to be used as scientific criteria. Stäubli[1] states that administration of levulose reduces the diabetic's tolerance for dextrose.

For the therapeutics of diabetes in greater detail the reader is referred to other sources.[2]

In this connection it may be mentioned that *d*-glucuronic acid and pentoses have a bearing on carbohydrate metabolism. A large variety of substances (camphor, chloral, turpentine) form syntheses with glucuronic acid in the organism, and corresponding glucuronates are then eliminated in the urine. At first glance glucuronic acid appears to be the preliminary oxidation product of glucose, as is suggested by the following equation:

$$\underset{\text{Dextrose.}}{OCH(CHOH)_4CH_2OH} + O_2 = \underset{\text{Glucuronic acid.}}{OHC(CHOH)_4COOH} + H_2O$$

However, Mandel and Jackson[3] administered camphor to fasting dogs for several days and noted the excretion of glucuronic acid. On giving large quantities of dextrose the protein metabolism fell and with it the glucuronic acid elimination; and on giving the animal chopped meat the quantity of camphoglucuronic acid in the urine was correspondingly increased. It may be safely inferred that glucuronic acid is produced solely in the intermediary metabolism of protein. For the large liter-

[1] Stäubli: "Deutsches Archiv für klin. Med.," 1908, Bd. cxiii, p. 125.

[2] Falta: "Ergebnisse der innere Medizin," 1908, Bd. ii, p. 74; Falta: Harvey Society Lecture, "Archives of Internal Medicine," 1909, vol. iii, p. 159; Janeway: "Am. Journal of the Medical Sciences," 1909, vol. cxxxvii, p. 313.

[3] Mandel and Jackson: "American Journal of Physiology," 1902, vol. viii. Proceedings of the American Physiological Society, p. xiii.

ature on this subject, and also on the pentoses, the reader is referred to other sources.[1]

Pentoses, which are sugars containing five atoms of carbon, have been detected in animal and vegetable tissue. Hammarsten found a pentose in the nucleoprotein of the pancreas. Neuberg showed that this pentose and the one obtained from nucleoprotein in the liver is *l*-xylose. Grund[2] has found pentoses in all organs of the body, particularly in those rich in nuclear material.

Salkowski and Neuberg have shown that *l*-xylose may be derived through ferment action on *d*-glucuronic acid. Salkowski was the first to detect a pentose in the urine, and this Neuberg has shown to be *i*-arabinose. The elimination of pentoses in the urine may accompany diabetes, but in extremely rare cases a simple pentosuria occurs in which pentose is the only sugar appearing in the urine.

Luzzatto[3] reports such a case in which the elimination of arabinose was independent of diet or mental or muscular effort. Luzzato believes the pentose in this case to have been *l*-arabinose. Neuberg finds that in the normal rabbit *l*-arabinose is more readily burned than *d*-arabinose. Luzzato's case could be explained by supposing that the body had lost its normal power to burn *l*-arabinose as normally produced in metabolism.

Pentosuria is occasionally discovered in the routine of life insurance examinations. So far as is known it does not indicate danger to general health.

Cremer,[4] in a series of excellent experiments, has shown that a vegetable pentose, such as rhamnose, may be burned in a rabbit and spare an isodynamic equivalent of fat. In one rabbit, on a fasting day, the total metabolism amounted to 129.1 calories (protein, 22.5, and fat, 106.6), and on the day when rham-

[1] Neuberg: "Ergebnisse der Physiologie," 1904, Bd. iii, 1 Abtheilung, p. 373.
[2] Grund: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv, p. 111.
[3] Luzzatto: "Hofmeister's Beiträge," 1904, Bd. vi, p. 87.
[4] Cremer: "Zeitschrift für Biologie," 1901, Bd. xlii, p. 428.

nose was given to 128.4 calories (protein, 21.36; fat, 32.9, and rhamnose, 74.11).

Lindemann and May[1] found that 90 grams of rhamnose could be used by a normal man. When, however, rhamnose was given to a diabetic individual whose urine had been sugar-free, sugar appeared in the urine. In cases of severe diabetes reported by von Jacksch[2] it was found that rhamnose, arabinose, and xylose tended to increase the protein metabolism, and hence the sugar output, and also brought about diarrhea. The use of pentoses in diabetes has therefore not been successful. The pentoses rhamnose, arabinose, and xylose are not convertible into dextrose in the organism.[3]

Opie[4] has endeavored to establish a connection between changes in the islands of Langerhans of the pancreas and the cause of diabetes. Janeway and Oertel,[5] von Noorden, and others, have reported autopsies on cases of severe diabetes in which the pancreas appeared perfectly normal. It is not always possible to observe with the microscope the cause of pathological change in function.

On autopsy in diabetes large quantities of fat are frequently found in the liver and muscles. The same is observed in chloroform narcosis when sugar appears in the urine, in anemia, and after respiration of rarefied air, where lactic acid is eliminated in the urine (p. 256), and in phosphorus- and arsenic-poisoning, in acute yellow atrophy, in pernicious vomiting of pregnancy, in eclampsia and in cyclic vomiting in children, which are similarly accompanied by an elimination of lactic acid. These phenomena are always associated with an increased protein metabolism and an increased ammonia and

[1] Lindemann and May: "Deutsches Archiv für klin. Med.," 1896, Bd. lvi, p. 282.

[2] Von Jacksch: *Ibid.*, 1899, Bd. lxiii, p. 612.

[3] Brasch: "Zeitschrift für Biologie," 1907, Bd. l, p. 113.

[4] Opie: "Journal of Experimental Medicine," 1901, vol. v, p. 397.

[5] Janeway and Oertel: "Virchow's Archiv," 1903, Bd. clxxi, p. 547.

amino-acid output in the urine.[1] Fat likewise appears in the mammary glands during lactation (p. 239).

Virchow assumed a fatty degeneration of protein in which the tissue protein was converted into fat, as distinguished from a fatty infiltration in which body fat passed into the cells. Much of the earlier writing of Voit is pervaded with the theory of a considerable origin of fat from protein (p. 142). The idea of a fatty degeneration of protein in the old sense has been largely overturned by the work of Rosenfeld.[2] Rosenfeld finds that if a dog be starved and then given sheep's fat, and again starved, the ingested fat will be found deposited as sheep's fat in his adipose tissue, while the liver will contain about 10 per cent. of fat, and this characteristic dog fat. If now phosphorus- or phlorhizin-poisoning be induced and the liver be examined, 40 per cent. of fat may be found therein, and this in the form of sheep's fat. Hence, in these cases the fat is simply transported to the liver from the fat deposits of the body. The fat in the blood is largely increased.[3] The fat becomes normal in quantity in the liver twenty-four hours after the cessation of the phlorhizin action. It is retransported to the places of fat deposit.

If a fatty "degeneration" were to be found anywhere, it would certainly be looked for in the dying cells of the phosphorus liver, or in the analogous condition of acute yellow atrophy of the liver. But another explanation avails.

Mandel and Lusk[4] have shown that lactic acid disappears from the blood and urine of a phosphorized dog if phlorhizin glycosuria be induced. The writer believes that the lactic acid which occurs is derived from the sugar formed in protein

[1] For literature consult Ewing: "Archives of Internal Medicine," 1908, vol. ii, p. 476.

[2] Rosenfeld: "Ergebnisse der Physiologie," 1903, Bd. ii, I, p. 50.

[3] B. Fischer ("Virchow's Archiv," 1903, Bd. clxxii, pp. 30, 218) reports a case of coma diabeticum in which the blood serum contained 23 per cent. of fat. Klemperer and Umber ("Zeitschrift für klinische Medizin," 1908, Bd. lxv, p. 340) state that of nine diabetics with acidosis seven had lipemia.

[4] Mandel and Lusk: "American Journal of Physiology," 1906, vol. xvi, p. 129.

metabolism. In the above case the sugar is removed without conversion into lactic acid. In phlorhizin diabetes, dextrose does not burn; in phosphorus-poisoning lactic acid derived from dextrose does not burn. In both cases a sugar-hungry cell, or one where carbohydrate is not oxidized, is found, and under these circumstances fat is attracted to the cell, and in larger quantities than can be useful. Wherever sugar freely burns this fatty infiltration is impossible (p. 166). A reduced local circulation in a portion of the heart may produce anemia of the part, an imperfect local oxidation of lactic acid normally formed, and a fatty infiltration of the locality. The writer offers this hypothesis as his explanation of fatty changes in tissue in general.

Present-day medical literature is frequently influenced by the idea of a reduced general oxidation in the body. Except in the case of myxedema which is accompanied by a fall in body temperature, and possibly in obesity, no such condition occurs. The writer[1] has shown that in phosphorus-poisoning, the classical example of supposed reduced oxidation, there was actually no reduction in the total heat production, but rather an increase due to a slight fever. From the fourth day to the sixth of simple fasting in one dog the total metabolism for twenty-four hours averaged 45.2 calories per kilogram, and on the ninth day to the eleventh of fasting which preceded death from phosphorus-poisoning the heat production was 48.8 calories.

It is therefore evident that the presence of lactic acid is only a symptom in the group of diseases just mentioned (p. 304) and is no more an indication of a reduction in oxidative power as represented by the total heat production than is the elimination of sugar in diabetes. The abundant ammonia in the urine is used to neutralize the acid produced. The reduction in the amount of lactic acid oxidized raises the total protein metabolism. The deficient deamination which results in the elimination of amino-acids in the urine may be due to the injury of

[1] Lusk: "American Journal of Physiology," 1907, vol. xix, p. 461.

deaminating enzymes by the presence of lactic acid; or it may be that deamination is difficult with certain amino-acids when it is not accompanied by oxidation with the formation of ketonic acids according to the formula given on p. 293; or it may be due to other unknown causes.

It has been stated that the action of phosphorus is to induce autolysis (self-digestion) of the body's protoplasm (Jacoby,[1] Waldvogel[2]), since leucin, tyrosin, glycocoll,[3] phenyl-alanin and arginin[4] and other amino-acids may be eliminated in considerable quantity in the urine. Wakeman[5] finds a change in the relative amounts of histidin, arginin, and lysin contained in the liver substance after phosphorus-poisoning, arginin in particular being reduced below the quantity found in the liver of the normal dog. Oswald[6] thinks that phosphorus destroys or weakens the antiautolytic agents of the body. That autolytic enzymes do not gain free control over the cells through the direct influence of phosphorus is proved by the work of Ray, McDermott, and Lusk.[7] These authors found that phosphorus injections raised the protein metabolism of fasting dogs to 250, 260, 283, 248, 183, and 164 per cent. of that of the dog when normal. They contrasted this increased protein metabolism with that obtained in phlorhizin glycosuria, which is represented by increases to 540, 450, 340, and 340 per cent. When, however, they gave phlorhizin and obtained the increased metabolism, and then injected phosphorus, *this was not followed by any marked increase in protein metabolism.* Under these circumstances phlorhizin glycosuria is the predominating factor, re-

[1] Jacoby: "Zeitschrift für physiologische Chemie," 1900, Bd. xxx, p. 174.

[2] Waldvogel: "Archiv für klinische Medizin," 1905, Bd. lxxxii, p. 437.

[3] Abderhalden and Bergell: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxix, p. 464.

[4] Wolgemuth: *Ibid.*, 1905, Bd. xliv, p. 74.

[5] Wakeman: "Zeitschrift für physiologische Chemie," 1905, Bd. xliv, p. 333.

[6] Oswald: "Biochemisches Centralblatt," 1905, Bd. iii, p. 365.

[7] Ray, McDermott, and Lusk: "American Journal of Physiology," 1899, vol. iii, p. 139.

moving the dextrose produced from protein before it could be converted into lactic acid. In this connection it may be stated that Laquer[1] finds no evidence of autolysis in the fresh livers of dogs which have died of acute arsenical poisoning, nor was the rate of autolysis in these livers in any way accelerated, an effect said by Jacoby to be characteristic of the livers of dogs which have died of phosphorus-poisoning. It seems therefore desirable to accept with caution this modern opinion which holds that in diseases such as those caused by metallic poisons where high protein metabolism is found there must of necessity be autolysis (or a condition in which proteolytic enzymes run riot) within the living protoplasm.

As regards phosphorus-poisoning Araki[2] believes that lactic acid accumulation is due to lack of oxygenation of the tissues caused by a slow heart-beat, but not due to anemia. He does not believe the oxygen deprivation to be very pronounced. The writer offers the explanation that phosphorus may affect the enzyme which breaks up the lactic acid derived from dextrose, and the accumulation of this acid may prevent the action of some of the deaminating enzymes; and, further, its non-combustion may necessitate an increase of protein metabolism.

This theory is strengthened by the discovery of Schryver[3] that the addition of lactic acid favors the accumulation of amino-acids in autolysis of the liver.

Claude Bernard showed that dextrose, whether derived from protein or starch, was convertible into glycogen, and this again was changeable into dextrose. Present knowledge adds lactic acid to both ends of this chain in showing the following possible progression of events—lactic acid, dextrose, glycogen, dextrose, lactic acid.

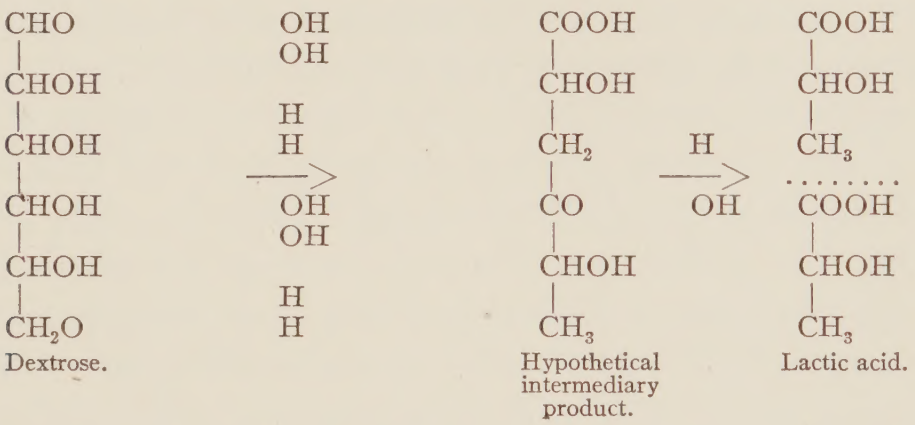
Quite pertinent to this theoretical discussion is the obser-

[1] Laquer: "Zentralblatt für Physiologie," 1909, Bd. xxiii, p. 717.
[2] Araki: "'Zeitschrift für physiologische Chemie," 1892, Bd. xvii, p. 337.
[3] Schryver: "The Bio-Chemical Journal," 1906, vol. i, p. 153.

vation of von Jaksch[1] on a patient who recovered from phosphorus-poisoning, and in whom a desire for carbohydrates marked the beginning of convalescence.

It should also be noted (see p. 180) that more carbohydrates must be ingested in cases of hepatic disease to maintain nitrogen equilibrium than are required in health.[2]

Regarding the normal destruction of dextrose Buchner and Meisenheimer[3] give the following picture of the production of lactic acid from it by hydrolytic changes.



The next step in the process is conjectural. Buchner believes that alcohol is formed. Walter Löb[4] suggests that lactic acid may be converted into acetol, CH_3 CO COOH, and then into formaldehyde, which latter is reconvertible into dextrose by the liver (p. 277). Or one may accept the idea of Magnus-Levy,[5] who found that if sugar were digested with aseptic liver tissue lactic acid, acetic acid, and butyric acid were formed with the evolution of hydrogen. The interpretation to be placed on this is that lactic acid yields acetic aldehyde and formic acid as follows:

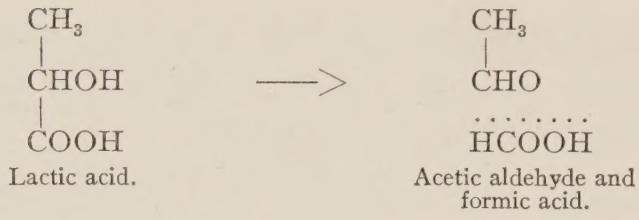
[1] Von Jaksch: "Zeitschrift für physiologische Chemie," 1903, Bd. xl, p. 123.

[2] Tallquist: "Archiv für Hygiene," 1908, Bd. lxv, p. 39.

[3] Buchner and Meisenheimer: "Berichte d. d. chem. Gesellschaft," 1904, Bd. xxxvii, p. 417.

[4] Löb: "Biochemische Zeitschrift," 1908, Bd. xii, p. 85.

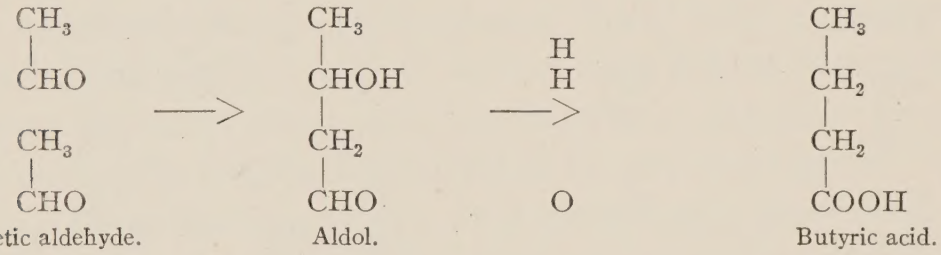
[5] Magnus-Levy: "Archiv für Physiologie," 1902, p. 365.



Lactic acid. Acetic aldehyde and formic acid.

The acetic aldehyde might then be oxidized or it might be condensed into aldol, which is β-oxybutyric aldehyde. From this butyric acid may arise, and with a larger number of acetic aldehyde molecules higher and higher fatty acids might be synthesized.

This chemical basis for the formation of fat from a product of dextrose metabolism may thus be written:



Acetic aldehyde. Aldol. Butyric acid.

Remembering former statements one sees an interesting play of the cells upon the molecule of lactic acid. At one time it is synthesized to sugar, at another it is broken down to form acetic aldehyde and this synthesized to higher fatty acid. When the system is flushed with carbohydrate and the glycogen repositories are charged with it, then one might picture the breaking up of carbohydrate into lactic acid and this to acetic aldehyde and formic acid, a condition in which the energy of the cell might be provided from the plentiful supply of formic acid while the acetic aldehyde molecules were condensed to form higher fatty acids.

CHAPTER XIII.

METABOLISM IN FEVER.

By fever is generally understood a complex of phenomena the dominant characteristic of which is a rise of body temperature. If the term fever be confined simply to the latter aspect, one might classify fevers as follows:

(1) *Physiological fever*, induced, for example, by immersion in a hot bath at a temperature of 40°, which prevents the normal loss of body heat through radiation and conduction. (2) *Neurogenic fever*, as brought about by the direct stimulation of nerve-cells in the *corpora striata* of the mid-brain. (3) *Non-infective surgical fever*, commonly called *aseptic fever*, due to the resolution of blood-cells or crushed tissue in the organism. (4) *Infective fever*, produced after the infection of the organism by certain bacteria or their products and by some protozoa. Or, one may consider fever as being due to infection by bacteria or protozoa, and include all other increases of temperature under the term of *hyperthermia*.

In a previous chapter the mechanism of normal heat regulation has been explained. It was there noted that on a warm, moist day the temperature of a fat individual, when he was working hard, rose considerably above the normal. This effect, if carried to an extreme, results in "*sunstroke*," where the overheating of the body causes a rapid pulse, accompanied by dizziness, delirium, or unconsciousness. But in the great majority of cases the body temperature remains delicately balanced, notwithstanding changes in outside environment, or internal heat production. In the fat person at hard work the condition of increased metabolism is combined with that of difficult discharge of heat. A person placed in a bath at 40° would be sub-

ject to conditions where there could be no heat loss, but rather a gain in heat, even though his metabolism were low. In a normal person, therefore, a rise in temperature may be due to increased heat production, with difficulty in discharging it, or a check of heat loss may be the only factor of the higher temperature. In the discussion of fever one must consider two possible causes: (1) an increase in heat production, and (2) a decrease in the facilities for the discharge of heat produced.

It has already been set forth that the metabolism in a cold-blooded animal increases with the temperature of his environment. Warmed tissue metabolizes more material than cooled tissue. It is therefore to be expected that the metabolism in an organism which has been warmed to fever heat will be greater than the normal. This was beautifully shown in the experiments of Pflüger,[1] who subjected both curarized and normal rabbits to external warmth which raised their temperatures. In the animals whose voluntary muscles were paralyzed by curare, as the rectal temperature rose from 39° to 41°, the oxygen absorption increased 10 per cent. for each degree of temperature increase. In the normal animals the increased metabolism between temperatures of 38.6° and 40.6° was shown by increases of 5.7 per cent. for oxygen, and 6.8 per cent. for carbon dioxid for a rise of one degree of temperature.

It has been noted in another chapter (p. 102) that Rubner found in man that a bath at a temperature of 35° had no effect on metabolism, while one at 44° increased the volume of respiration 18.8 per cent., the oxygen absorption 17.3 per cent., and the carbon dioxid elimination 32.1 per cent. Linser and Schmid[2] confirm these results in experiments on two men suffering from *ichthyosis hystrix*, which involved almost complete loss of function of the sweat glands. The body temperature of these men could be varied by altering the temperature of their living-room

[1] Pflüger: "Pflüger's Archiv," 1878, Bd. xviii, pp. 303, 356.

[2] Linser and Schmid: "Archiv für klinische Medizin," 1904, Bd. lxxix, p. 514.

between 30° and 38°. The humidity of the room was from 40 to 50 per cent. The maximum increase in the metabolism of these individuals is represented by a rise in carbon dioxid excretion from 3.8 c.c. per minute and kilogram at the body temperature of 36.2° to 5.3 c.c. per minute and kilogram at 39°. The number of respirations, which were from 12 to 15 per minute at 36°, increased to 20 and 22 at 39°. The total increase in the carbon dioxid output, due to a rise of 3° through simple warming of cells, amounted to 40 per cent.

The next question is of the nature of the materials which are oxidized. It has long been known that urea excretion is abnormally high in fever, and this led to the inquiry whether the rise was merely the result of increased body temperature or was due to toxic influences. Thus, Schleich[1] finds that a man in nitrogen equilibrium is affected by an hour's bath in water between 40.5° and 41.5° which causes his temperature to reach 39.7°, so that his nitrogen metabolism for the day increases 18, 22, and 37 per cent. Other authors have not found any increase, but Linser and Schmid[2] explain these divergences of opinion by showing that an increase of body temperature to 39° in man has no effect on protein metabolism, but that above this there is always an increased destruction of protein. They therefore conclude that in toxic fevers where the temperature is not above 39° any increase of protein metabolism must be due to the toxic processes and not to the hyperthermia.

F. Voit[3] found that on artificially raising the temperature of a fasting dog to 40° or 41° for a period of twelve hours, there was an increase in nitrogen elimination of 37 per cent. above the normal. Warming for a period of only three hours had slight effect. If, however, the animal were fed with meat and fat, warming increased the protein metabolism only 4 per cent.

[1] Schleich: "Archiv für ex. Path. und Pharm.," 1875, Bd. iv, p. 90.

[2] Linser and Schmid: *Loc. cit.*

[3] Voit, F.: "Sitzungsberichte der Gesellschaft für Morphologie und Physiologie," 1895, Heft ii, p. 120.

If the animal were given 30 to 40 grams of cane sugar, no increased metabolism of protein followed the rise in temperature to 41°. It is apparent that the ingestion of protein and carbohydrates may control this rise in protein destruction due to a febrile temperature. F. Voit explains the increase in protein metabolism in hyperthermia as due to the quick combustion of glycogen and the consequent impoverishment of the tissues as regards carbohydrate material. Protein or carbohydrate ingesta furnish the necessary carbohydrate and prevent the hyperthermal rise in protein metabolism. The destruction of protein due to toxic processes cannot be so easily controlled, as will be seen later.

If certain portions of the brain be punctured, and particularly the region of the *corpora striata*, a high fever sets in. Here again there is an increased output of carbon dioxid and a rise in protein metabolism. This phenomenon has been recently investigated by Hirsch, Müller, and Rolly[1], and by Rolly[2] alone. They find that after the "heat puncture" of the corpora striata the liver, blood, and skin become warmer than the muscles, although normally the muscles are warmer than the skin. They find that the heat puncture is effective even in curarized animals, where the muscles are free from nerve stimuli. Rolly finds, however, that the heat puncture is ineffective if the liver of the rabbit has been previously freed from glycogen by strychnin convulsions. Under these circumstances there is no rise in temperature nor concomitant rise in protein metabolism. The inference is that the fever in question is due to nerve impulses which increase the metabolism of carbohydrate in the liver. In infectious fever there is little glycogen in the organism, but that the fever in this case is due to other causes than the rapid combustion of carbohydrates was shown by Rolly, who infected a rabbit, which had been freed from glycogen as above described, with a culture of pneumococci and obtained as great a rise in

[1] Hirsch, Müller, and Rolly: "Deutsches Archiv für klin. Med.," 1903, Bd. lxxv, p. 264.

[2] Rolly: *Ibid.*, 1903, Bd. lxxviii, p. 250.

temperature and protein metabolism as would have occurred had the tissues of the rabbit been rich in carbohydrates. The rise in temperature after puncture of the corpora striata may be termed *neurogenic fever*, and it is like the glycosuria following Claude Bernard's puncture, in that its mechanism is no more invoked in true infectious fever than are the nerve centers in diabetes mellitus (p. 272).

If the extent of metabolism in infectious fevers be investigated and compared with that found in simple hyperthermia, a closely analogous state of affairs is discovered. The course taken by the metabolism in toxic fevers is, as a rule, (1) a slight rise in protein metabolism, even before the fever sets in; (2) increased metabolism with heat retention and increased protein destruction; (3) heat production and heat outgo become equal, with the body at a higher temperature level. These factors are illustrated in the experiments of May[1] on fasting rabbits injected with a culture of erysipelas of the pig. The results of these respiration experiments with three rabbits, in which the normal, transition, and fever periods were investigated, are given below.

METABOLISM IN FEVER IN RABBITS (*May*).

Rabbit.	Day of Fast.	Body Temperature.	Calories.			
			Total.	From Protein.	From Fat.	Remarks.
E.....	3	39.2–39.5	61.9	18	44	Normal.
	4	39.7–41.2	63.9	19	45	Injection.
	5	41.2–40.7	73.3	27	46	Fever.
G.....	3	38.5–38.2	53.8	16.8	37	Normal.
	4	38.2–38.6	54.0	18.5	35.6	"
	5	38.6–38.6	55.4	20.6	34.8	Injection.
	6	38.7–40.1	61.2	27.9	33.3	Fever.
H.....	3	39.0–39.6	64.5	10.7	53.8	Normal.
	4	39.6–39.2	64.2	10.4	53.7	"
	5	39.7–41.0	65.8	11.8	54.0	Injection.

[1] May: "Zeitschrift für Biologie," 1894, Bd. xxx, p. 1.

The above table shows a slight increase in the protein metabolism on the day of infection. It also shows that a high fever may be reached by the end of the twenty-four hours after the injection without materially altering the heat production of the day. It demonstrates that on the day of continued fever the metabolism increases, and this at the expense of an increased destruction of protein, while the fat consumption remains unaltered. A calculation shows that on the days of high fever 20 per cent. more energy was produced in rabbit E, and 15 per cent. more in rabbit G, than on normal days. Since Traube's writings on the subject were published, the cause of fever has been attributed, not to great heat production, but to a disturbance in the mechanism for the regulation of heat loss. On recalling the fact that the metabolism of a fasting dog may be raised from 100 calories in starvation to 189 calories after giving meat (p. 153), without any change of body temperature, it becomes evident that the rise in metabolism in fever is too insignificant to be the cause of the rise in temperature. In fact, as has been already set forth, the rise in body temperature from failure of the physical regulation may of itself explain the increase in heat production. Thus a calculation made in the case of rabbit E shows that the carbon dioxid elimination is increased 6.6 per cent. for each degree of rise in temperature, which corresponds to Pflüger's experiments, before mentioned, in which artificially warmed normal rabbits excreted 6.8 per cent. more carbon dioxid for each degree of rise in temperature.

Staehelin[1] infected a dog by inoculating him with 1.5 c.c. of dog's blood containing surra trypanosomes which are active flagellate parasites. Fever set in on the sixth day after the inoculation and the dog died on the twenty-fifth day. The metabolism due to the infection rose to 88.9 calories per kilogram on the tenth day after inoculation as against a normal of 59.8, an increase of 48 per cent. On this febrile day 26 per cent. of the total energy was yielded by protein; the body lost 2.8 grams

[1] Staehelin: "Archiv für Hygiene," 1904, Bd. l, p. 77.

of nitrogen which indicated a high toxic waste. However, all the increase in the heat production did not come from increased protein metabolism as in the case of May's rabbits, but the fat destruction was also increased, and Staehelin speaks of a toxic waste of fat. He also remarks that the dog remained perfectly quiet during the period of the experiment, but he does not say whether thermal influences which could result in chill were completely excluded. However, he came to the conclusion that in this fever caused by trypanosomes the metabolism was higher than could be explained by the over-warming of the body, an explanation which sufficed in the case of May's rabbits.

During the last days of life the body temperature fell and with it the amount of the metabolism. The following table gives a partial record of the daily metabolism in this dog:

METABOLISM IN FEVER INDUCED BY SURRA TRYPANOSOMES.

Period.	Day after Inoculation.	No. of Days in Period	Grams N in Food.	Grams N to Body.	Calories in Food.	Calories of Metabolism.	Calories per Kg.	Calories per Sq. M. Surface.	Body Temp.	
									Max.	Min.
I. Normal (average)..	..	..	5.67	+ 0.15	585	510.0	59.8	1027	..	..
II. Inoculation and prodromal.....	6	6	5.67	— 0.18	585	469.3	58.3	982	39.4	38.3
III. 1st of fever.....	7	4	5.67	— 0.40	585	521.4	63.9	1081	39.5	38.3
	8	..	5.67	— 0.46	585	556.9	68.2	1154	39.6	37.7
	9	..	5.67	— 1.06	585	675.2	81.6	1388	40.1	39.6
	10	..	5.67	— 2.80	585	729.3	88.9	1507	39.2	37.9
IV. 2d of fever (average).....	11–17	7	4.37	— 2.50	451	665.2	83.7	1404	..	..
V. 3d of fever (average).....	18–20	3	3.34	— 2.52	348	665.0	74.0	1218	40.4	38.5
VI. Final period (average).....	21–24	4	—	— 4.63	..	521.0	62.0	907	38.8	35.5

Long before May's experiments, Wood[1] had found an average increase of 23 per cent. (calculated by Welch) in the heat production of fasting dogs after inducing fever; and he

[1] Wood: "Fever," Philadelphia, 1880.

also found that mere ingestion of food by a normal dog would cause a greater heat production than fever itself.

Traube attributed the cause of fever to a cramp-like constriction of the peripheral arterioles which prevented the proper distribution of blood at the surface, and therefore hindered the normal cooling of the body.

The effect of a cold bath upon a vigorous man is to constrict the peripheral blood-vessels and to increase the heat production. The body temperature, instead of falling, may rise for eight or ten minutes and then sink.[1] If the individual pass from the bath during the earlier minutes the hot blood comes to the surface to be cooled, and the body glows with a red color, the so-called "reaction." This experiment shows that there are factors invoked during the first few minutes which prevent the discharge of the heat produced. One factor must be a general constriction of the peripheral arteries, causing the blood to remain in the heat-producing inner organs of the body. In this experiment, therefore, cooling of the organism is prevented by the mechanism of physical regulation above described, and the mechanism of chemical regulation which reflexly increases heat production.

To combat a rise in temperature, however, the only means available is the physical regulation,—*i. e.*, the change in the distribution of the blood and the production of sweat. If these avenues of heat loss be diminished or shut off, heat accumulates within the body and temperature rises. Why an increase in heat production of 89 per cent. may not cause a rise in temperature in a normal animal has already been explained; whereas, a high fever may be accompanied by an increased metabolism of only 15 per cent. The cause of the fever must therefore be a diminution in the ability to discharge the heat produced.

In further support of this, Senator has shown that the fever following pus injections in a dog begins with a retention of heat within his body. Nebelthau[2] found in a rabbit that during the

[1] Lefèvre, J.: "Comptes rendus soc. biol.," 1894, T. xlvi, p. 604.

[2] Nebelthau: "Zeitschrift für Biologie," 1895, Bd. xxxi, p. 353.

first twelve hours of infection in which the temperature rose from 38.6° to 40.1°, the discharge of heat was but 96.3 per cent. of that of the previous period. Assuming the heat production to have been the same in these two periods (as was actually the case in the rabbits of May), then the retention of heat would account for the pathological increase in temperature. At a later stage the discharge of heat rose to equalize its production at the higher temperature.

Nebelthau has shown a fall in temperature and heat production in a rabbit whose cord was divided between the sixth and seventh cervical vertebræ, and has also demonstrated that under these circumstances infection with erysipelas of the pig had no influence on temperature or heat production. The inference is that the febrile toxins act through the higher vasomoter centers, whose regulatory control is lost in the above experiment.

A kindred interpretation may be placed on the experiments of Mendelson,[1] who was unable to produce fever through pus injections when the dog was under the influence of chloral or morphin, although such treatment in a normal animal caused a rise in temperature of from 36.3° to 39.9° in forty-five minutes. Mendelson also finds a constant constriction of the renal blood-vessels in fever.

Further experimentation convinced Sawadowsky[2] that fever cannot be produced after the mid-brain has been severed from the medulla, whereas if the mid-brain be left intact, but the cerebrum be sectioned from it, fever may be induced in the ordinary course. The toxic substance must therefore act on nerve-cells in the mid-brain, which in turn stimulate the medullary centers.

At times during high fever the skin may be red and the peripheral blood-vessels distended. Although there is no sufficient explanation for the continuance of fever when the radiation and conduction of heat from the surface of the body are

[1] Mendelson: "Virchow's Archiv," 1885, Bd. c, p. 274.

[2] Sawadowsky: "Centralblatt für medizinische Wissenschaft," 1888, Bd. xxvi, p. 161.

thus increased, Krehl[1] suggests that the quantity of blood flowing through the vessels at the time may be inadequate to reduce the body's temperature.

The second means of physical regulation of the body temperature is through the evaporation of water from both the lungs and the sweat glands. It might be surmised that the activity of this mechanism was reduced in fever. Nebelthau[2] has shown that the heat lost by evaporation of water, and by radiation and conduction, bear exactly the same ratio to each other in normal and in fever-infected rabbits. Since Rubner (p. 98) has proved that the elimination of water in normal animals greatly increases at high temperatures, the mere maintenance of the usual water evaporation during fever would of itself be abnormal.

No complete metabolism experiment on a man suffering from high fever has ever been made, and here is an opportunity for some one to perform a rare service. By no means the least interesting phase of such an experiment would be the course of water elimination from the skin.

Lang[3] has shown that the elimination of sweat is reduced during the rise of temperature in man, but at the height of fever is the same as the normal, while there is some increased evaporation from the lungs.

Recent experiments by Schwenkenbecker and Inagaki[4] show that the "insensible perspiration" in fever is as great as in health, and that although the urine may decrease in quantity there is no actual accumulation of water in the body as was believed by von Leyden (see p. 331).

Lang[5] has also shown that the secretion of sweat is increased 50 per cent. after the ingestion of food as against an increase of 70 per cent. in the normal individual.

[1] Krehl: "Pathologische Physiologie," 1904, p. 453.

[2] Nebelthau: *Loc. cit.*

[3] Lang: "Archiv für klinische Medizin," 1903, Bd. lxxix, p. 343.

[4] Schwenkenbecker and Inagaki: "Archiv für ex. Path. und Pharm.," 1906, Bd. liv, p. 168.

[5] Lang: *Loc. cit.*

In intermittent fever profuse perspiration is certainly an important factor in the reduction of temperature at the end of the febrile stage.

It may be concluded, as Krehl[1] emphatically states, that insufficiency of water evaporation plays a not unimportant rôle in the febrile rise in temperature. The body might be cooled were the sweat glands freely active.

The production of heat in fever may be greatly increased during a chill, and a rapid rise in temperature may follow. This was shown by Liebermeister[2] in a case of malaria. The temperature rose from 36.9° in the first half hour to 39.5° at the end of another hour, while the carbon dioxid expired rose from 13.85 grams to 34.20 grams per half hour. This was a case of chill with shivering. This increased metabolism is due to the mechanism of chemical regulation. The blood is driven from the skin by vaso-constriction, those end-organs of the skin which are sensitive to cold are strongly stimulated, with the result that there is a reflex increase of heat production. That this is true is shown by the fact that if the cold stimulation be removed by supplying a warm environment, the attending phenomena pass off (Krehl).[3]

Any muscular exercise, such as sitting up, increases metabolism, and may under some circumstances cause a rise in temperature in fever. (Compare with effect of tetanus, p. 270.) The diurnal variation of temperature is similar in character to that of health, but its fluctuations are much more extreme, on account of the increased excitability of the vasomotor control of the discharge of heat. The parallelism between the amount of the metabolism and the height of the temperature during the day is shown in Fig. 10, taken from Riethus.[4]

It is apparent that cold and muscular work increase metab-

[1] Krehl: "Clinical Pathology," 1907, p. 403.

[2] Liebermeister: "Deutsches Archiv für klinisches Medizin," 1871, Bd. viii, p. 153.

[3] Krehl: "Pathologische Physiologie," 1904, p. 452.

[4] Riethus: "Archiv für ex. Path. und Pharm.," 1900, Bd. xliv, p. 239.

olism and temperature in fever, and it may be also surmised that large protein ingestion, which by its specific dynamic action increases heat production, will likewise increase the

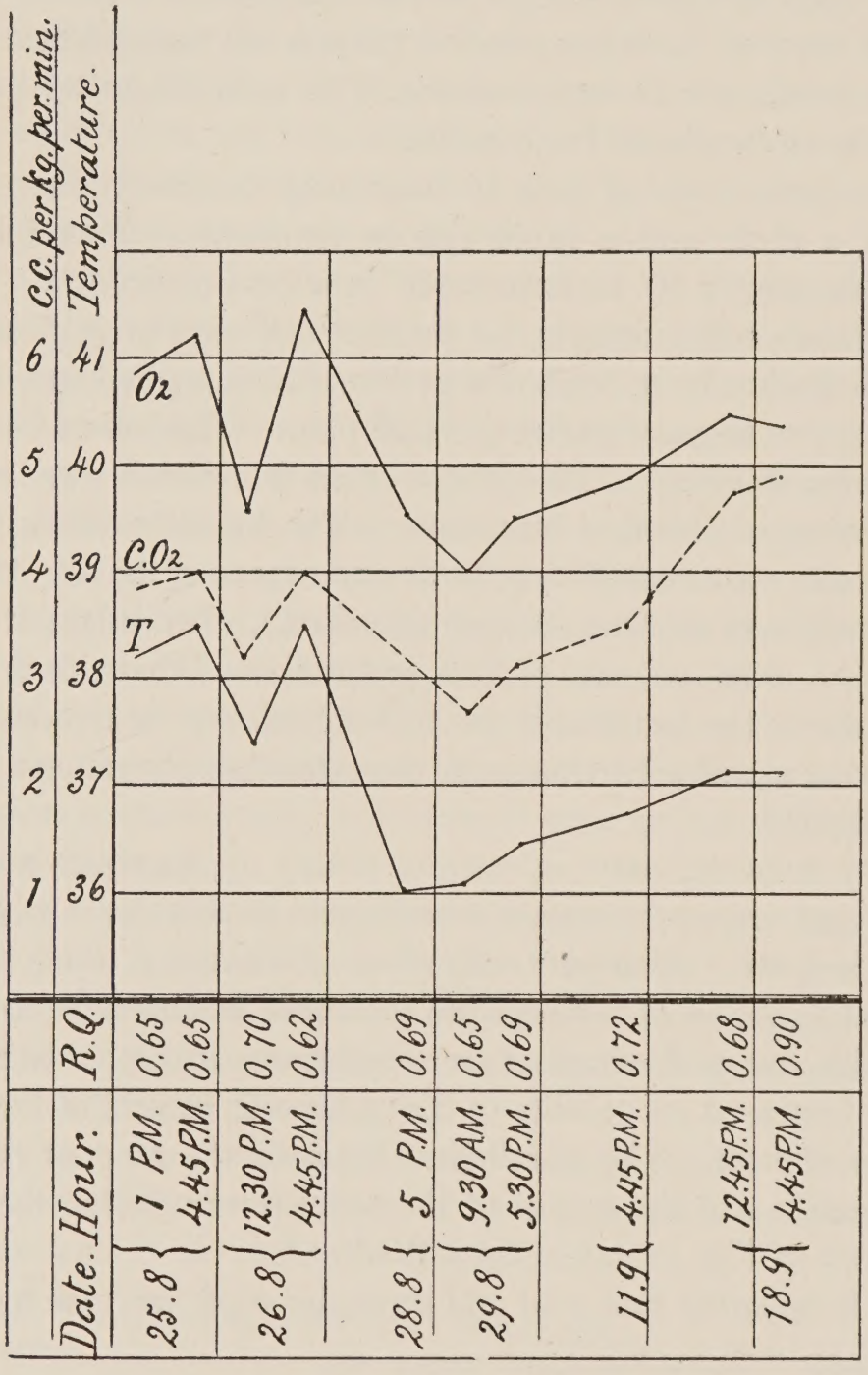


Fig. 10.—Case of abdominal typhoid (Riethus). The figures 1 to 6 on the left represent the amount in c.c. of CO_2 and O_2 of respiration per kilogram and minute. The measurements were all made during fasting. The O_2 curve may be considered as nearly proportional to the heat production (p. 33).

body's temperature at a time when heat discharge is difficult (p. 163).

May[1] summarizes the conditions of metabolism in fever in the following statement: "There is an increased protein metabolism but no increased fat metabolism, except such as may incidentally result from dyspnea, chill, or muscular activity."

Infectious fevers are characterized by a toxic destruction of body protein. Sometimes, as in the earlier stages of tuberculosis, this tissue destruction may be present in the absence of fever itself. Such a toxic action on body protein is also observed in cancerous cases, as was described by Fr. Müller.[2] Müller writes: "In the seven cases (of carcinoma) cited, the nitrogen excretion was larger than the nitrogen ingestion and consequently the body lost protein. In two cases the protein loss was no greater than in healthy individuals with similar insufficient nourishment. In all the other cases the protein metabolism was decidedly above that of healthy men under the same conditions. Even an ample dietary was not able to establish nitrogen equilibrium. As more food was given the nitrogen elimination rose higher and higher, but the point of nitrogen equilibrium seemed unattainable." Müller compared the cachexia of carcinoma with that found in febrile processes and believed them to be analogous.

As regards tuberculosis May[3] writes: "Larger quantities of the toxins produce, with certain exceptions, a direct injury to the cell protoplasm. They are strongly toxic. The quantity of protein destruction attributable to this cause is not very large and becomes of importance only when continued for a long period of time and where there is no compensatory regeneration. It appears that the power to regenerate on the part of these cells which are destroyed by toxins is greatly reduced and in severe cases entirely lost."

[1] May: Ott's "Chemische Pathologie der Tuberculose," 1903, p. 355.
[2] Müller, F.: "Zeitschrift für klinische Medizin," 1889, Bd. xvi, p. 496.
[3] May: Ott's "Chemische Pathologie der Tuberculose," 1903, p. 335.

Other fevers show a high toxic destruction of protein. F. Müller[1] reports a daily loss of 10.8 grams of nitrogen (equal to 318 grams of muscle) by a typhoid patient during eight days of fever. During fever in croupous pneumonia, the protein metabolism is much higher than normal. After the crisis there is still a large excretion of nitrogen in the urine which continues until the croupous exudate has been decomposed by autolysis, absorbed by the blood, and metabolized in the body (epicritical nitrogen elimination). In acute pneumonic phthisis (galloping consumption), with its caseous transformation of lung tissue, there is a very high waste of tissue protein. F. Müller[2] has shown that while the croupous exudate readily undergoes autolysis at a temperature of 40°, with the production of deutero-albumoses, lysin, leucin, tyrosin, etc., the caseous mass does not undergo autolysis although it permits free diffusion of soluble material, such as phosphates. Hence, although the protein of the cheesy mass is insoluble in the organism, the soluble toxins may be absorbed from the diseased part, and be the causative agent of the rapid destruction of body protein in galloping consumption.

The above analysis of metabolism in fever shows that the small increase in total metabolism is associated with increases in protein metabolism due (1) to the high temperature, and (2) to the virulence with which toxins attack the body tissue. It has been shown that carbohydrate ingestion may reduce the protein destruction due to the overheating, and that toxic destruction may or may not be compensated for by regenerative processes. Upon this general knowledge it is possible to construct a dietary schedule for the patient.

In all fevers the septic products act upon the hunger centers in the brain, and appetite is wanting. This is evidenced throughout the course of tuberculosis, for example, and tends in

[1] Müller, F.: "Centralblatt für klinische Medizin," 1884, No. xxxvi.

[2] Müller, F.: "Verhandlungen des 20 Congresses für innere Medizin," 1902, p. 192.

this case to weaken the body's resistance through undernutrition. Forced feeding is therefore resorted to.

The experiments of von Hösslin[1] strongly affirmed the beneficence of a liberal diet in ordinary fevers. He writes: "The results show that febrile patients, or at least those who do not run temperatures above 40° to 40.5°, can digest and absorb the total amount of protein, fat, and carbohydrates which can be given them with their diminished appetite, provided the food is administered in a proper form. Temperature and metabolism are only slightly increased thereby."

A milk diet is the usual course prescribed in fevers. Since milk is the proper diet for a rapidly growing calf, its protein content is extremely high. The relative quantity of this ingredient may be reduced by modifying the milk through the addition of milk sugar or cream. In this way von Leyden and Klemperer[2] have added 5 per cent., then 7.5, and finally 10 per cent. of milk sugar to whole milk. The last named quantity raises the calorific value by 410 calories per liter, and makes a milk containing 1050 calories per liter. Two liters of such milk would be nearly or quite sufficient to cover the requirement of an individual confined to his bed. A milk so prepared may be given to most patients without producing diarrhea or indigestion. The taste is perfectly agreeable to the patient. In this way carbohydrates, which are highly desirable in the febrile condition, can be properly administered. Von Leyden and Klemperer have also found that an addition of cream to milk, so that its value is increased by 2.5 per cent. of fat, or 225 calories per liter, is favorably received by the patient. Such a milk diet may be fortified by the addition of brandy, whiskey, or sherry. This increases the calorific value of the milk, but more particularly gives it taste, and both through the awakening of the sense of appetite and through direct action upon the neuro-secretory

[1] Von Hösslin: "Virchow's Archiv," 1882, Bd. lxxxix, p. 317.

[2] Von Leyden and Klemperer: Von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 345.

apparatus of the digestive tract, favorably influences the digestion of the food.

It seems strange that in this country where so much attention has been paid to the modification of infant food, the preparation of suitable diet in fever should have received such scant attention. It may well be that investigation will show that dilution of milk and its fortification by ingredients other than protein may be as advantageously practised in fever cases as in infant nutrition.

The discussion now turns from these theoretical considerations to the actual results of nutritive investigations in fever as presented by von Leyden and Klemperer.

The following table represents a case of a typhoid fever patient to whom milk fortified with meat powder was given, thereby producing a high protein diet. The quantity of the individual nutrients, the calorific value of the diet, and the nitrogen in the urine and feces were determined. The daily loss of body nitrogen was calculated. The results were as follows:

METABOLISM IN TYPHOID; DIET HIGH IN PROTEIN.

Highest Temp.	Food.					Excreta.			Loss of Body N.
	Amount in Grams.	Calories.	N.	Fat.	Carbohydrates.	Urine N.	Feces N.	Total N.	
39.6	600 milk.	408	3.2	21	27	15.76	0.42	16.18	12.98
39.8	1000 milk.	680	5.36	35	45	18.96	0.42	19.38	14.02
40.2	900 milk. 20 meat-powder.	686	7.67	31	40	17.88	0.42	18.30	10.63
39.7	1200 milk. 50 meat-powder.	1002	13.61	42	54	21.56	1.75	23.31	9.70
39.9	1500 milk, 100 meat-powder.	1392	22.45	52	67	28.7	1.75	30.45	8.00
40.3	1200 milk, 50 meat-powder.	1188	20.86	42	54	27.9	1.75	29.65	8.79
40.3	1500 milk, 50 meat-powder.	1206	15.2	52	67	21.7	1.92	23.92	8.42
39.8	2000 milk, 50 meat-powder.	1546	17.85	70	90	22.9	1.92	24.82	6.97
40.2	2000 milk, 100 meat-powder.	1732	25.1	70	90	29.6	1.92	31.52	6.42
39.9	2000 milk, 50 meat-powder.	1546	17.85	70	90	20.85	2.13	22.98	5.13
39.8	1200 milk, 50 meat-powder.	1002	13.61	42	54	19.76	2.13	21.89	8.28
39.9	1500 milk,	1020	8.0	52	67	15.86	2.13	18.02	10.02

It will be noted that there was a large loss of body nitrogen on every day of the experiment. Even when the diet contained 25.1 grams of nitrogen, the excreta of the day contained 31.5 grams, indicating a loss of 6.4 grams from the body. The days of the smallest loss of tissue nitrogen were those on which the largest quantity (90 grams) of carbohydrates was given. Also a diet containing 17.85 grams of nitrogen seems to protect the protein waste about as well as one with 25.1 grams of nitrogen when both diets contain equal quantities of carbohydrates and fat.

Von Leyden and Klemperer regard the above experiment as indicating the advantage of a large protein ingestion in preventing tissue waste. But deficient calorific value and lack of carbohydrates may be accountable for the increased waste on the lower protein diets. It must also be remembered that protein itself yields carbohydrate in metabolism. That carbohydrates of themselves cannot prevent the toxic waste of protein tissue is apparently illustrated in another experiment given by the same authors. The case was again one of typhoid, and carbohydrates were given in large quantity:

METABOLISM IN TYPHOID; DIET HIGH IN CARBOHYDRATE.

Highest Temp.	Food.					Excreta.		
	Quantity in Grams.	Calories.	N in Grams.	Fat in Grams.	Carb. in Grams.	Urine N in Grams.	Feces N in Grams.	Loss of Body N in Grams.
39.8	2808 milk, 400 lactose, 60 glucose, ½ liter sherry.	3020	14.9	98	386	20.1	1.5	6.7
39.7	2768 milk, 200 lactose, 133 glucose, ½ liter sherry.	3295	14.6	96	457	19.7	1.5	6.6
38.8	2460 milk, 300 lactose, ½ liter sherry.	2952	13.0	86	411	23.7	1.3	12.0
40.2	2366 milk, 300 lactose, ½ liter sherry.	2892	12.5	83	406	23.3	1.2	12.0
39.6	2430 milk, 109 lactose, ½ liter sherry.	2522	12.8	85	310	23.7	1.3	12.2
38.8	2080 milk, 200 glucose, ½ liter sherry,	2420	11.1	80	303	21.8	1.1	11.8
39.2	1870 milk, 200 glucose, ½ liter sherry.	2141	9.9	65	344	19.4	1.0	9.5

In this case it is apparently shown that a moderate amount of protein, combined with a large quantity of fat and carbohydrates of large energy content, does not in any way prevent the constant waste of body tissue in typhoid fever. Since it has been demonstrated that carbohydrates prevent tissue destruction due to hyperthermia, it must be assumed that the nitrogen waste is here due to toxic destruction of the cells.

May, from his work upon fasting rabbits already alluded to, concluded that the increased protein metabolism in fever was in large measure due to the absence of available carbohydrate, and not primarily to a toxic waste of tissue. Thus in one rabbit he was able to diminish the nitrogen elimination during fever from 2.43 grams to 1.29 grams by giving 30 grams of dextrose, a reduction of 47 per cent.

The efficiency of a carbohydrate diet in typhoid fever has been splendidly demonstrated by Shaffer,[1] who has shown that the ingestion of large amounts of carbohydrate in a low protein diet may completely or almost completely maintain the patient in nitrogen equilibrium throughout the disease. The diet consisted of milk, milk sugar, diluted cream, eggs and sometimes arrowroot starch. Shaffer writes: "It was only when we gave 60, 70, or even 80 calories per kilogram of bodyweight—between 3000 and 4000 calories—that the greatest sparing was observed."

Dr. Shaffer has kindly allowed the use of heretofore unpublished reports on two individuals suffering from typhoid (see table on p. 329).

From this it may be concluded that nitrogen equilibrium may be very nearly maintained throughout the course of typhoid fever on a diet containing 12 to 15 grams of nitrogen, provided an excess of carbohydrate beyond the requirement of the organism be also administered. Very likely under these circumstances the fat in the diet is without influence, except that it is retained in the organism. As to whether the presence of carbo-

[1] Shaffer: "Journal of the American Medical Association," 1908, vol. li, p. 974.

hydrates prevents the toxic waste of body protein, or provides conditions for a compensatory regeneration, Dr. Shaffer is not willing to express an opinion.

INFLUENCE OF CARBOHYDRATES ON METABOLISM IN TYPHOID FEVER.

SUBJECT I.

Period.	No. of Days in Period.	Range of Maximum Temp. During Period.	Total Calories of Food.	Calories per Kg.		Nitrogen in Food.	Nitrogen to Body.
				Total.	From carbohydrates		
I.	4	104 –103.2° F.	4280	72	48.	13.9	— 0.9
II.	6	103.6–102.8° F.	5200	85	48.	15.0	— 0.2
III.	4	103.8–103.4° F.	2750	45	7.	15.0	— 8.5
IV.	8	104.8–101.4° F.	5340	89	52.	14.5	— 2.8
V.	6	100.8– 99.4° F.	4990	83	48.	13.8	+ 1.2
VI.	4	Normal.	2430	41	7.	13.5	— 0.3

SUBJECT II.

I.	9	104.4–102.6° F.	1920	31	7.8	12.6	—11.3
II.	6	102.8–100.6° F.	4290	70	47.	12.6	*— 1.1
III.	6	Normal.	1930	32	8.	12.7	— 3.8
IV.	8	102.8– 99.6° F. Relapse.	4800	78	50.	14.1	+ 3.6
V.	6	Normal convalescence.	2460	39	12.	14.6	+ 1.8

*Average for last three days of diet.

It is apparent that a large ingestion of protein is unnecessary, in typhoid at least, and it should be avoided on account of its extra heat-producing power—its specific dynamic action.

An illustration of the course of nitrogen metabolism in a different fever—namely, pneumonia—may also be taken from von Leyden and Klemperer. The details are given on p. 330.

In this case it is apparently demonstrated that nitrogen equilibrium cannot be obtained during high fever, and also that the loss of body nitrogen does not cease at the crisis, but rather continues on account of the epicritical elimination of nitrogen derived from the protein of the croupous exudate. During the time of this epicritical elimination the body appears

unable to add new protein to itself. About four days after the crisis, true convalescence begins with the upbuilding of new protein tissue.

METABOLISM IN PNEUMONIA.

Temp. on Successive Days.	Food.					Excreta.			Loss of Body N.
	Quantity in Grams.	Calories.	N.	Fat.	Carbohydrates.	Urine N.	Feces N.	Total N.	
40.8 (highest).	2000 milk.	1360	10.6	70	90	24.7	0.9	25.6	15.0
40.9 (highest).	2000 milk, 150 cream, 100 lactose.	1980	11.4	85	197	22.8	0.9	23.7	12.3
41.2 at 12 M. 36.8 at 7 P. M.	2000 milk, 150 lactose.	1975	10.6	70	240	21.7	0.9	22.6	12.0
37.3 (highest).	2000 milk, 200 cream.	1612	11.7	90	99	21.9	1.1	23.0	11.3
36.8 (highest).	2000 milk, 200 cream, 2 eggs.	1752	13.7	100	99	18.5	1.1	19.6	5.9
36.8 (highest).	2000 milk, 300 cream, 4 eggs.	2018	17.3	120	104	18.7	1.1	19.8	2.5

On autopsy of patients who have died of fevers, parenchymatous and fatty degenerations of the organs have been found. These changes have been ascribed to overheating of the cells.

Litten[1] warmed guinea-pigs artificially and noted fatty but no parenchymatous degeneration of the tissues. The space in which the animals were kept was, however, insufficiently ventilated, and the fatty change might have been caused by dyspnea, as results in normal animals (p. 257).

Naunyn[2] observed that rabbits might be artificially warmed for thirteen days so that an average body temperature of 41.5° was maintained without any parenchymatous or fatty degeneration taking place. The animals were supplied with ample food, water, and a sufficient supply of air. Naunyn found that the red blood-cells of rabbits and dogs remained intact even at a body temperature of 42°. Welch[3] noticed fatty but no paren-

[1] Litten: "Virchow's Archiv," 1877, Bd. lxx, p. 10.

[2] Naunyn: "Archiv für ex. Path. und Pharm.," 1884, Bd. xviii, p. 49.

[3] Welch: "Medical News," 1888, vol. lii, p. 403.

chymatous change in the tissues of rabbits after exposure to high temperature for at least a week. One rabbit which had been subjected to high temperature for four days was inoculated with the bacilli of the swine plague and died in thirty-six hours showing extreme fatty changes in the heart and other organs.

Ziegler[1] discovered degenerative changes, both parenchymatous and fatty, on artificially warming rabbits. The experiment was continued in one case for twenty-nine days. He found, however, a great reduction (30 per cent. and more) in the quantity of hemoglobin in his rabbits. It may well be a question whether the fatty change noticed in the liver and muscles was not due to anemia instead of to the hyperthermia. Since fatty infiltration is known to be caused by dyspnea, which frequently terminates life in fever, one might investigate this subject to see whether parenchymatous change in fever is not solely due to the toxins, and fatty change to the anaërobic cleavage of materials in the cells, which always induces fatty infiltration (p. 304).

Ever since the experiments of von Leyden[2] a retention of water in fever has been assumed. It has also been shown that there is a retention of sodium chlorid within the body. The intimate relation between the retention of water and salt has been beautifully demonstrated by Sandelowsky[3] in Lüthje's clinic. Thus during the period of high fever in pneumonia, a gain in weight, a sodium chlorid retention, and a dilution of the organic contents of the blood usually went hand in hand. After the crisis, however, a loss in weight, a loss of chlorid, and a more concentrated blood resulted. Similar conditions were found in scarlet fever.[4] Sandelowsky observed that when sodium chlorid was given to a patient convalescent from pneumonia, it was not as readily eliminated by the kidney as it would have been normally. From this he concluded that a disturbed

[1] Ziegler: "Kongress für innere Medizin," 1895, Bd. xiii, p. 345.
[2] Von Leyden: "Deutsches Archiv für klin. Med.," 1869, Bd. v, p. 273.
[3] Sandelowsky: "Deutsches Archiv für klin. Med.," 1909, Bd. xcvi, p. 445.
[4] Oppenheimer and Reiss: *Ibid.*, p. 464.

renal condition existed during fever, and was not wholly restored to the normal after the crisis. This brought about sodium chlorid retention, which in turn caused water retention, that the normal osmotic conditions might be preserved. This accounts for the gain in body-weight and the loss in the concentration of the blood in fever.

As regards the etiology of fever, various attempts have been made to identify a single factor which would cause the high temperature.

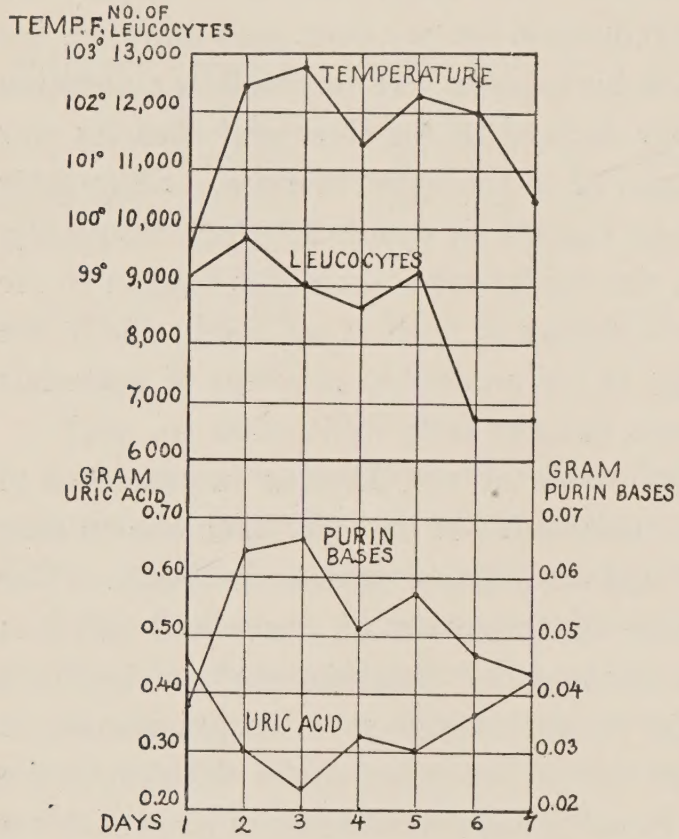


Fig. 11.—Resection of knee-joint for tubercular arthritis.

Krehl and Matthes[1] find that human urine during fever contains an increased quantity of albumoses which have been shown to possess a decidedly toxic action when introduced into animals. Klemperer[2] denies that these albumoses have any toxic action and asserts that the results were due to impurities in preparation. In other respects the urine has generally been found to be of normal character. Thus Mohr[3] finds that the relation C to N in the urine is unchanged from the normal, which indicates that there is no qualitative change in the character of the general protein metabolism.

[1] Krehl and Matthes: "Archiv für klinische Medizin," 1895, Bd. liv, p. 501.
[2] Klemperer: "Naturforscherversammlung," 1903, 2, ii, p. 67.
[3] Mohr: "Zeitschrift für klinische Medizin," 1904, Bd. lii, p. 371.

However, there is a very noteworthy record made by A. R. Mandel[1] that the rise of temperature in so-called aseptic or surgical fevers is accompanied by a large increase in the purin bases in the urine of patients fed with milk. The temperature rises and falls with the quantity of purin bases eliminated. The uric acid elimination is reduced (p. 346). These relations are illustrated in Fig. 11,—a case of resection of the knee-joint for tubercular arthritis. The temperatures recorded represent the average of observations made every three hours during the day.

That the purin bases can be the cause of the rise of temperature is indicated by the experiments of Burian and Schur,[2] who found that when nucleoprotein was administered intravenously to a dog, a rise of temperature followed. Mandel showed that a subcutaneous injection of 40 milligrams of xanthin caused a marked rise in the temperature of a monkey, and that the administration of a strong decoction of 60 grams of coffee (containing trimethyl-xanthin) to a man unused to coffee drinking was followed by a febrile temperature. This is shown in Fig. 12.

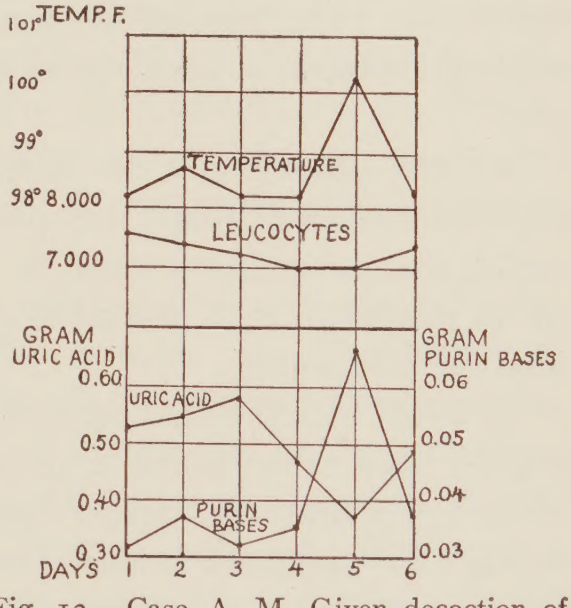


Fig. 12.—Case A. M. Given decoction of 60 gms. coffee.

Another research available in this connection is that of von Jaksch,[3] who noted that the purin bodies in the urine of tuberculous patients may increase from a normal equivalent of 4.4 per cent. of the total nitrogen excreted, to one representing

[1] Mandel: "American Journal of Physiology," 1904, vol. x, p. 452.
[2] Burian and Schur: "Pflüger's Archiv," 1901, Bd. lxxxvii, p. 239.
[3] Von Jaksch: "Zeitschrift für klinische Medizin," 1902, Bd. xlvii, p. 1.

11.3, or even 17.39 per cent. Also Benjamin[1] reports a case of typhoid where the urine contained the large quantity of 0.1 gram of purin bases with 0.54 gram of uric acid. Erben[2] and Leathes[3] report that the output of uric acid is always increased during high fever. Erben also finds that the content of the urine in xanthin bases and amino-acids is greatly augmented in measles and chicken-pox; and that the xanthin bases are also increased, though to a lesser extent, in scarlet fever and typhoid. Mandel[4] has fed monkeys with bananas and xanthin and witnessed a rise in body temperature, and has noticed that if sodium salicylate be given at the same time no rise in temperature occurs. Ott[5] reports that guanin, adenin, and hypoxanthin cause an elevation of temperature in rabbits, while uric acid does not.

Mandel believes that the purin bases liberated through the toxic destruction of tissue may play a considerable part in producing the temperatures noted in fever. It is evident that the use of purin-free milk instead of purin-containing meat has its scientific justification.

It would indeed be a most striking fact if it should be found that the cause of the febrile temperature lies in the effect of purin bases on the heat-regulating apparatus of the mid-brain acting through the vasomotor system. Antipyretics do not lower body temperature in the normal organism in man. Is their action merely to nullify the activity of purin bases upon the nerve centers? Future research alone can decide this. Such conjectures indicate the extraordinary field which lies open to the investigator in clinical medicine.

[1] Benjamin: "Salkowski's Festschrift," 1904, p. 61.
[2] Erben: "Zeitschrift für Heilkunde," 1904, Bd. xxv, p. 33.
[3] Leathes: "Journal of Physiology," 1907, vol. xxxv, p. 205.
[4] Mandel: "American Journal of Physiology," 1907, vol. xx, p. 439.
[5] Ott: "The Medical Bulletin" (Medico-Chir. College), October, 1907.

CHAPTER XIV.

PURIN METABOLISM.—GOUT.

Uric acid was discovered in urinary calculi by Scheele in 1776, and was found to be present in gouty concretions by Wollaston in 1797. It has since been the subject of investigations almost without number, and of theoretical speculation beyond that of any other chemical substance described in medical literature. The older work concerning the excretion of uric acid is almost valueless on account of the inadequacy of the chemical methods of the times. Accurate determinations of uric acid date from the introduction of a new method of analysis by Salkowski in 1882.

The newer researches are also based on more exact chemical knowledge of the precursors of uric acid. Much valuable information has been gathered as regards the normal method of production of uric acid, although it will be seen that on the pathological side there is little beyond the conjectural to reward the student.

Emil Fischer[1] grouped together uric acid, hypoxanthin, xanthin, adenin, and guanin as bodies whose varying structure depended upon slight changes around the chemical nucleus of a substance called purin. Purin, according to Fischer, may occur in the body, but on account of its ready decomposability, has not been discovered there.

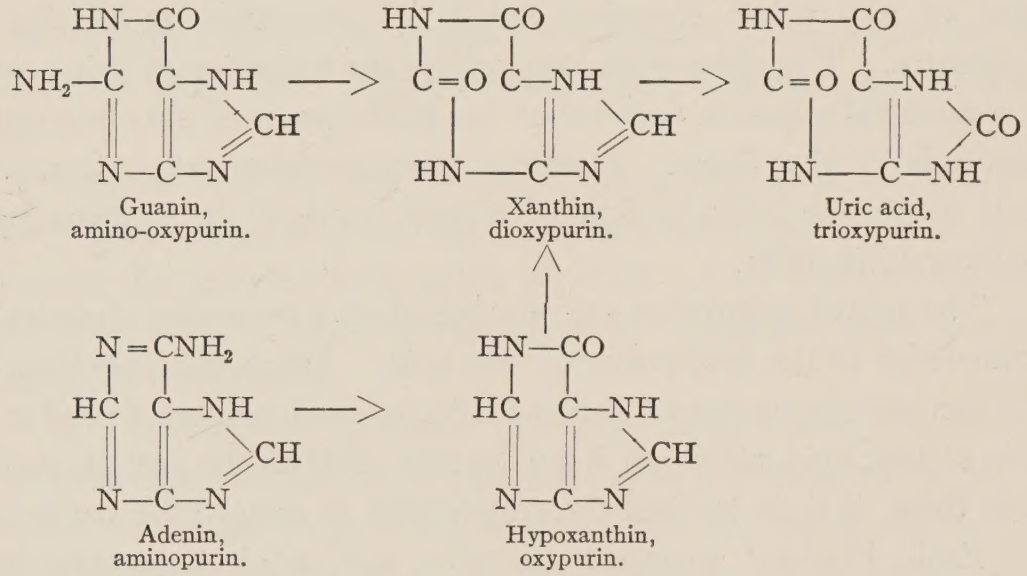
The relations between the purin bodies may be judged from the following formulæ:

Purin	$C_5H_4N_4$
Hypoxanthin	$C_5H_4N_4O$
Xanthin	$C_5H_4N_4O_2$
Uric acid	$C_5H_4N_4O_3$
Adenin	$C_5H_3N_4NH_2$
Guanin	$C_5H_3N_4ONH_2$

[1] Fischer: "Berichte der deutschen chemischen Gesellschaft," 1899, Bd. xxxii, p. 435.

Hypoxanthin, xanthin, and uric acid are respectively mono-, di-, and tri-oxypurin. Adenin is aminopurin, and guanin is aminohypoxanthin. It is evident that uric acid is the most highly oxidized product of the series, and might readily arise from the oxidation of hypoxanthin and xanthin. It is also apparent that by supplanting the NH_2 group in adenin and guanin by O, they would be converted into hypoxanthin and xanthin respectively, and that from these substances uric acid might arise through oxidation.

These reactions may be thus expressed:



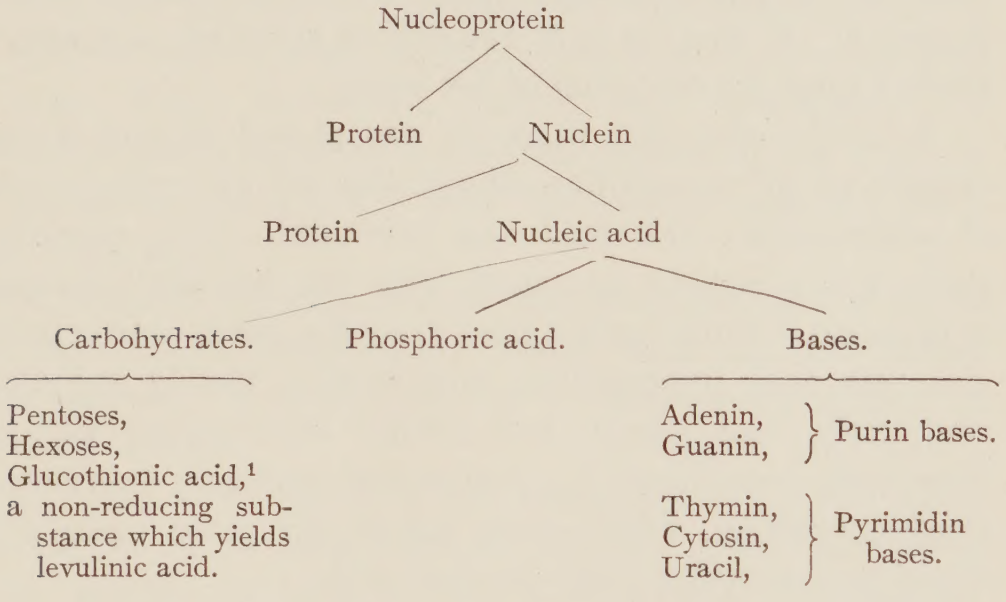
The deamination of guanin and adenin is accomplished by hydrolysis and may occur in the absence of oxygen, whereas the conversion of hypoxanthin into xanthin and the latter into uric acid are true processes of oxidation.

For greater detail of the chemistry of purins, the reader is referred to any text-book on physiological chemistry.[1] The four precursors of uric acid, hypoxanthin, xanthin, adenin, and guanin are collectively called the *purin bases*. The general term, *purin bodies*, includes uric acid also.

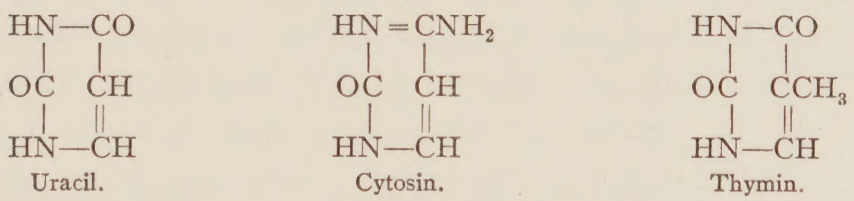
Since Salomon discovered, in 1880, that purin bases exist

[1] Consult also Mendel: "The Formation of Uric Acid," Harvey Society Lecture, "Journal of the American Medical Association," 1906, vol. xlvi, p. 843.

in the nucleins which are present in the nuclei of cells, a great deal of work has been done to explain the chemical nature of these nuclear constituents. A summary of the products which can be obtained from nucleoproteins is as follows:



The formulæ of the pyrimidin bases are:



Kossel and Steudel[2] point out the fact that the purin bases contain the pyrimidin nucleus, and that cytosin, for example, needs only cyanic acid, CONH, and an atom of oxygen, to convert it into uric acid.

They query whether the pyrimidin bases are precursors or metabolized products of the purins, but the question is still unsettled.[3]

[1] Mandel and Levene: "Zeitschrift für physiologische Chemie," 1906, Bd. xlvii, p. 151.

[2] Kossel and Steudel: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxviii, p. 49.

[3] Consult Abderhalden: "Lehrbuch der physiologischen Chemie," 1909, p. 381.

Horbaczewski[1] was the first to note that the ingestion of nucleins largely increased the uric acid in the urine. Food free from nuclein has not this effect. He also found that if fresh spleen pulp, which contains no uncombined purin bases, be permitted to putrefy, xanthin and hypoxanthin made their appearance. If now the pulp was shaken in the air, uric acid was formed from the oxidation of the bases.

Spitzer[2] found that when air was passed through aqueous extracts of spleen and liver digested at 40° and with exclusion of putrefaction, uric acid was produced. The quantity of purin bases present decreased with the increased formation of uric acid. Purin bases added to such a digest were converted into uric acid, hypoxanthin, and xanthin readily and almost completely, and guanin and adenin with greater difficulty. This work established the presence of oxidizing enzymes, the xanthin oxidazes, which could act on the purin bases in the organism converting them into uric acid.

Minkowski[3] has shown that if a man be given hypoxanthin, the quantity of uric acid increases in his urine. He also showed that if a man ingest thymus gland, the nuclein of which yields principally adenin, the amount of uric acid is increased in the urine. If the thymus be given to a dog, the uric acid plus allantoin elimination is increased. Allantoin is an oxidation product of uric acid more frequently found in dog's than in human urine. Minkowski discovered finally that adenin, when administered to a dog, did not increase the uric acid elimination, and was not excreted as such, but on autopsy of the dog the uriniferous tubules were found to contain crystals the chemical structure of which showed them to be aminodioxypurin. In other words, adenin administered combined in nucleic acid loses its amino (NH_2) group, receives three atoms of oxygen,

[1] Horbaczewski: "Sitzungsberichte der Wiener Academie der Wissenschaft," 1891, Bd. c, Abth. iii, p. 13.

[2] Spitzer: "Pflüger's Archiv," 1899, Bd. lxxvi, p. 192.

[3] Minkowski: "Archiv für ex. Path. und Pharm.," 1898, Bd. xli, p. 375.

and is thereby converted into uric acid; adenin administered as such receives two atoms of oxygen but does not lose its NH_2 group at the point for the attachment of the third atom of oxygen. This work attests a varying behavior of purin bodies in accordance with their method of chemical union with other substances, and offers a suggestive key to certain relations observed in gout (p. 353). When theophyllin, caffein, and theobromin, the methylated purins found in tea, coffee, and cocoa, are ingested they are not oxidized to uric acid, but they increase the purin bases in the urine.[1]

The original investigations of Horbaczewski have recently been considerably extended by Schittenhelm and by Walter Jones, especially in regard to their explanation along lines of enzymotic activity.

Jones and Partridge[2] find that although the great majority of the organs of the body, when self-digested at 40° (autolysis), convert guanin and adenin into xanthin and hypoxanthin, presumably through the action of enzymes, extracts of the spleen of the pig cannot convert guanin into xanthin, although they can convert adenin into hypoxanthin. Jones therefore concludes that an enzyme, guanase, which normally removes the NH_2 group and replaces it with O, is wanting in the pig's spleen, while adenase, the enzyme acting on adenin in a similar fashion, is present there. Such a reaction would read:

$$\underset{\text{Adenin.}}{C_5H_3N_4NH_2} + H_2O = \underset{\text{Hypoxanthin.}}{C_5H_4H_4O} + NH_3$$

Investigating the subject further, the authors found that the pancreas contained the enzyme, guanase, which converts guanin into xanthin.

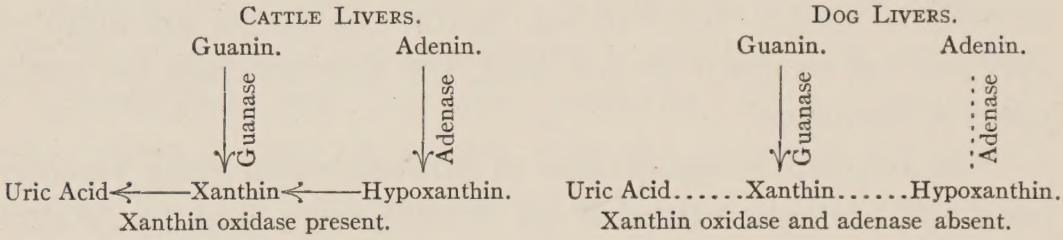
The behavior of the livers of different animals has been investigated by Jones and Austrian.[3] In cattle livers, for ex-

[1] Krüger and Schmid: "Zeitschrift für physiologische Chemie," 1901, Bd. xxxii, p. 104.

[2] Jones and Partridge: *Ibid.*, 1904, Bd. xlii, p. 343; see also Levene: "American Journal of Physiology," 1904, vol. xii, p. 276.

[3] Jones and Austrian: "Zeitschrift für physiologische Chemie," 1906, Bd. xlviii, p. 110.

ample, adenase, guanase and xanthin oxidase are present, whereas in dog livers guanase is present, adenase occurs in traces only, and no xanthin oxidase whatever has been found. Hence cattle livers may form uric acid from adenin and guanin, while dog livers only convert guanin into xanthin and the other processes are arrested. The process is thus graphically represented:



Furthermore these authors find that guanase is absent from pigs' livers, while adenase and xanthin oxidase are present. It is interesting that Mendel and Mitchell[1] have found in the liver of the embryo pig at an early age the same specific enzymes as characterize the liver of the adult animal. There was, however, a considerable delay in the appearance of the enzyme which oxidizes uric acid (see below). It is a curious phenomenon that pigs suffer from guanin gout. Their normal urines contain uric acid,[2] but it may be surmised that in guanin gout the enzyme guanase is wanting.

Schittenhelm[3] reports that human livers have the power to form uric acid from added purins and he believes that the power to oxidize uric acid exists.

Lauder Brunton[4] says that Stockvis, of Amsterdam, in 1860, found that crushed tissue had the power to destroy uric acid. This question has recently come into prominence and it has been shown that different organs have different powers

[1] Mendel and Mitchell: "American Journal of Physiology," 1907, vol. xx, p. 97.

[2] Schittenhelm and Bendix: "Zeitschrift für physiologische Chemie," 1906, Bd. xlviii, p. 140.

[3] Künzel and Schittenhelm: "Zentralblatt für Stoffwechsel," 1908, Bd. iii, p. 721.

[4] Lauder Brunton: "Centralblatt für Physiologie," 1905, Bd. xix, p. 5.

in this regard, and that the same organ in animals of different species may behave quite differently.

Wiener[1] showed that dog's liver and pig's liver destroyed uric acid, whereas calf's liver had less power to do so, or none at all. The kidney pulp of various animals also destroyed uric acid.

Schittenhelm[2] finds that in cattle the spleen, lungs, liver, intestine, and kidney have the power of converting purin bases into uric acid in the presence of a constant oxygen supply. He finds a complete transformation of adenin, as follows: adenin, hypoxanthin, xanthin, uric acid. Guanin in like manner becomes xanthin and this again is converted into uric acid. He finds also that extracts of the spleen, intestines, and lungs have no power to destroy uric acid as formed within them, but that the kidney, muscle, and liver extracts possess the power to destroy the new-formed uric acid.

Schittenhelm[3] in another paper finds that kidney extracts from cattle, through which oxygen is passed, may completely destroy uric acid through a uricolytic enzyme.

It has been shown by Pfeiffer[4] that the pulps of human kidneys and pigs' kidneys have the power to destroy uric acid completely, while dogs' kidneys have only a limited capacity in this regard.

Almagia[5] finds that in the horse the greatest power of uric acid destruction is possessed by the liver, and then follow in order of diminishing activity the kidney, lymphatic glands, leukocytes, muscles, bone-marrow, spleen, and thyroid. In other organs, like the brain and the pancreas, the conditions are such as indicate a non-destruction of uric acid, which is produced by the oxidation of purin bases within them.

Summarizing these results it may be said that nucleic acid

[1] Wiener: "Archiv für ex. Path. und Pharm.," 1899, Bd. xlii, p. 375.

[2] Schittenhelm: "Zeitschrift für physiologische Chemie," 1905, Bd. xlv, p. 145.

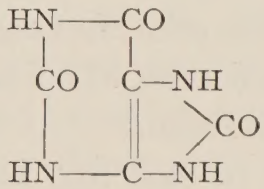
[3] Schittenhelm: *Ibid.*, 1905, Bd. xlv, p. 161.

[4] Pfeiffer: "Hofmeister's Beiträge," 1905, Bd. vii, p. 463.

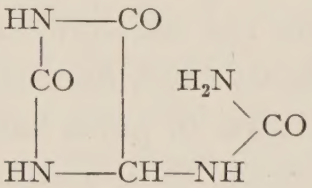
[5] Almagia: "Hofmeister's Beiträge," 1905, Bd. vii, p. 459.

may be broken up by nuclease, a ferment found in all tissue. On the liberation of the purin bases, guanin and adenin are deaminized by guanase and adenase wherever these enzymes are found. Oxidizing enzymes, the xanthin oxidases, now convert hypoxanthin and xanthin into uric acid, while a uricolytic ferment of varying potency in different tissues and in different animals may break up and destroy the uric acid. That processes akin to these go on within the living organs of the body is now generally believed, and the following animal experiments tend to confirm this doctrine, although it will become evident that the uricolytic power of kidney extracts, so frequently mentioned above, appears to be entirely overshadowed in the living kidney by the function of uric acid elimination.

It has already been stated that the ingestion of hypoxanthin by a man increased the uric acid output in the urine. It has long been known that if uric acid be given *per os*, it may in greater part be converted into urea, and in part eliminated in the urine. The quantity eliminated varies in different animals. Salkowski[1] finds that uric acid given to dogs is mostly eliminated as urea, although 17.7 per cent. appears in the urine in the form of allantoin. When uric acid is given to rabbits the urine contains urea, allantoin, and some uric acid. Mendel and White[2] found that allantoin was eliminated in the urine of cats and dogs after intravenous injection of urates. The relationship between uric acid and allantoin is evident from the following formulæ:



Uric acid.



Allantoin.

It is usually believed that uric acid is largely destroyed in

[1] Salkowski: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv p. 495.

[2] Mendel and White: "American Journal of Physiology," 1904, vol. xii, p. 85.

animals such as cats, dogs, and rabbits, and that a portion of an intermediary product of oxidation, allantoin, appears in the urine. However, Wiechowski[1] states that uric acid digested with the pulp of dog's liver is oxidized completely into allantoin and no further; and also that uric acid injected subcutaneously into a dog is almost completely eliminated as allantoin in the urine. He does not show that purin bases ingested normally behave in the same manner.

Schittenhelm and Bendix[2] have injected rabbits subcutaneously and intravenously with guanin, and have found uric acid in greatly increased quantity in the urine, together with xanthin, which is normally absent in rabbits. The experiment indicates the metabolism of guanin *intra vitam*, according to processes already observed *in vitro*. If an Eck fistula, which excludes the portal blood from the liver, be made in a dog, uric acid appears in considerable quantity in the urine, which indicates that uric acid is normally oxidized in the dog's liver.[3]

Burian and Schur,[4] after careful perusal of the literature and of their own work, came to the conclusion that each variety of animal had a specific capacity for burning purin bodies ingested. They found a constant elimination in dog's urine of one-twentieth part of the purins ingested, one-sixth part in the case of rabbits, and one-half in the case of man. They describe how Minkowski, after giving a man hypoxanthin, saw that 48.6 per cent. of it was eliminated as uric acid; how Burian repeated the experiment with the result that 46.2 per cent. appeared as uric acid; how the subject of the last experiment eliminated 51.1 and 53.8 per cent. of the purins contained in a meat diet, and 52.6 and 52.9 per cent. of those contained re-

[1] Wiechowski: "Hofmeister's Beiträge," 1907, Bd. ix, p. 295; 1908, Bd. xi, p. 109.

[2] Schittenhelm and Bendix: "Zeitschrift für physiologische Chemie," 1905, Bd. xliii, p. 365.

[3] Hahn, Massen, Nencki, and Pawlow: "Archiv für ex. Path. und Pharm.," 1893, Bd. xxxii, p. 191.

[4] Burian and Schur: "Pflüger's Archiv," 1901, Bd. lxxxvii, p. 239.

spectively in calf's liver and calf's spleen. Therefore, Burian and Schur multiplied the purin excretion of a man by two and of a dog by twenty in order to determine the total purin metabolism. They called these numbers the *integral factors* of purin excretion. The cause of the size of the integral factor will be discussed later.

It has been made clear that the purin bodies may be derived from ingested nucleins, but this cannot be the only source, since purins are found in the urine during starvation and on a diet free from purins. This indicates a constant production of these substances in metabolism, it has been thought, through the destruction of cell nuclei. Uric acid and purin bases from this source have been termed *endogenous* by Burian and Schur, in contradistinction to those which are eliminated after the ingestion of nuclein-containing food, which are called *exogenous*.

Burian and Schur[1] also established the fact that while the endogenous uric acid elimination varied between 0.3 and 0.6 gram daily, according to the individual, it did not vary in the same individual but was a constant factor of his metabolism.

A purin-free diet is obtained by giving such articles of food as milk, eggs, bread, potatoes, fats, and sugars, none of which contain nuclear material which forms exogenous purins in the body. Burian and Schur found that on such a diet the uric acid elimination was entirely independent of the quantity of protein ingested. It has been demonstrated by Rockwood[2] that the endogenous uric acid elimination is independent of the calorific value of the diet. Addition of 500 calories contained in maple sugar to a diet containing 2500 calories did not affect the excretion of uric acid. Rockwood's experiments extended over a long period of time. His individuals were nourished on milk, eggs, white bread, crackers, cheese, apples, and butter. The constancy of the uric acid output in the same individual is

[1] Burian and Schur: *Loc. cit.*

[2] Rockwood: "American Journal of Physiology," 1904, vol. xii, p. 38.

seen in the following table,—in one case the record covering nearly a year:

TABLE SHOWING THE CONSTANCY OF THE DAILY ENDOGENOUS URIC ACID EXCRETION IN THE SAME INDIVIDUAL (TWO SUBJECTS).

Person, A.	Date, 1903.	N in Urine, Grams.	Uric Acid, Grams.
	January	11.99	0.308
	February	11.58	0.305
	March	11.15	0.315
	May	12.63	0.321
	July	12.68	0.313
	November	9.99	0.298
Person, B.	January	13.41	0.478
	March	13.92	0.452

This total shows the constancy of the output of endogenous uric acid in the same individual during a long period. Here the difference in the behavior of two individuals might possibly be ascribed to a personal idiosyncrasy as regards the uricolytic power of the subject, or to a difference in the capacity of producing uric acid. From the record of Chittenden's[1] experiments, which covered a period of twenty-one months, it may be observed that a very low protein diet and moderate intake of food were without effect on the output of uric acid.

Burian and Schur[2] have made a series of experiments as regards the cause of the "integral factor" of purin metabolism, which has already been defined. They find that a part of the endogenous purins are burned in metabolism, for the uric acid elimination in the dog rises largely after cutting the liver from the circulation by means of an Eck fistula. They note that no one has been able to find uric acid in normal blood. They desired to see if uric acid would accumulate in the blood if the kidneys were both extirpated. No such result followed nephrectomy in a dog. The purin bodies were apparently completely burned. They then extirpated the kidneys and ligated the aorta at a point just above the celiac artery. The operation cut

[1] Chittenden: "Physiological Economy in Nutrition," 1904, p. 24.

[2] Burian and Schur: *Loc. cit.*

off the liver and intestine from the circulation. Under these circumstances uric acid accumulated in the blood because its destruction was not accomplished by the liver. The question arises: If the normal organism can completely destroy all purins, why should a definite fraction be continually eliminated in the urine? Burian and Schur believe that endogenous purins, formed in the tissues, are oxidized therein to uric acid, and in so far as this substance is carried to such organs as the liver, it is destroyed, but in so far as it passes through the renal arteries, it is removed by the kidney. In confirmation of this they show that a diuretic which increases the blood-flow to the kidney may likewise increase the uric acid elimination, without affecting the other nitrogenous constituents of the urine. Possibly the fall in uric acid elimination noted by Mandel in aseptic fever (p. 332, Fig. 11) may be similarly due to a constriction of the renal vessels which may accompany fever (p. 319).

Burian and Schur conclude that of the mass of blood which receives uric acid from the tissues in man, the same amount flows through the organs which destroy uric acid as flows through the kidney, and hence the integral factor of two. On the other hand, the relation between the volume of kidney blood and the volume of blood passing through the organs which destroy uric acid in dogs must be as 1 : 20 in order to explain the integral factor twenty. At first sight this does not explain why exogenous purins, which must pass from the intestine to the dog's liver, should escape complete destruction in that organ. Burian and Schur, however, have shown that whereas uric acid given *per os* is almost completely destroyed in the dog, the purin bases or the products of nucleoprotein digestion containing them apparently pass through the liver to be oxidized to uric acid elsewhere.

The liver has the power of oxidizing uric acid but not the purin bases. Hence the behavior of exogenous purins must be exactly the same as if they arose in the general metabolism of the tissues themselves and were oxidized to uric acid, which

was then carried in definite fractions, in accordance with the relative volume of the blood supply, either to the kidney for elimination or to the organs where uric acid is destroyed.

This explanation of the cause of the integral factor would explain the results of Loewi,[1] which showed that the ingestion of the same amount of nuclein-containing food by different people resulted in the excretion of the same increased quantity of uric acid in the urine. However, Loewi at the time was inclined to believe that the uric acid which was produced in the human being was not oxidized, and this opinion was apparently confirmed by the discovery of Soetbeer and Ibrahim,[2] who found that the subcutaneous injection of uric acid in man resulted in its complete elimination in the urine. This view is also held by Wiechowski,[3] who has further shown that allantoin injected subcutaneously is completely eliminated in human urine which is normally free from it. Schittenhelm[4] criticizes these ideas and maintains that uric acid introduced into the blood stream might behave differently from uric acid arising from purins which had been ingested. In the latter case their partial destruction has been demonstrated.

The theory of a fixed integral factor is not supported by Landau's[5] experiments upon eight human beings. Landau concludes that the amount of the elimination of exogenous purins (mostly uric acid) is different in different individuals and varies between 37 and 91 per cent. of the purins ingested. He believes that these differences depend on differences in the intensity of the uricolytic power of the various subjects. He found that the quantity of exogenous uric acid which underwent oxidation depended upon the character of the purin material

[1] Loewi: "Archiv für ex. Path. und Pharm.," 1900 ,Bd. xliv, p. 1.

[2] Soetbeer and Ibrahim: "Zeitschrift für physiologische Chemie," 1902, Bd. xxxv, p. 1.

[3] Wiechowski: "Archiv für experimentelle Path. und Pharm.," 1909, Bd. lx, p. 185.

[4] Künzel and Schittenhelm: "Zentralblatt für Stoffwechsel," 1908, Bd. iii, p. 721.

[5] Landau: "Deutsches Archiv für klinische Medizin," 1909, Bd. xcv, p. 280.

given. Hypoxanthin when ingested uncombined was more largely excreted as uric acid than were purins contained in nucleoprotein. The latter, on account of their complicated structure, were only slowly broken up and the uric acid from them appeared less rapidly in the blood than if free purins had been ingested, and therefore there was a more complete oxidation and a reduced elimination.

The source of the endogenous purins has been the cause of considerable speculation. In birds there is a large synthetic production of uric acid in the liver, for Minkowski[1] has shown that extirpation of the liver in geese leads to a replacement of uric acid by ammonia and lactic acid in the urine. In the developing organism there is a production of purins for the construction of the nuclear content of the cells. The method of production is entirely conjectural.

Ingestion of pyrimidin bases (p. 337) has failed to yield purins in the organism.[2]

Burian[3] has investigated the source of the endogenous purins and comes to the conclusion that only a small part of the endogenous uric acid arises from the nucleoproteins of cellular tissue or those of dead leukocytes. It would require too large a destruction of tissue to provide from 0.3 to 0.6 gram uric acid or 0.1 to 0.2 gram purin nitrogen daily in the urine if it all arose from cell nuclein.

Burian and Schur's[4] analyses, showing the content of purin nitrogen in various tissues, are given below.

TABLE SHOWING THE QUANTITY OF PURIN N CONTAINED IN 100 GRAMS OF DIFFERENT ANIMAL TISSUES.

	Total Purin N.	N in Free Purin Bases.
Meat	0.06	0.045
Thymus	0.45	0.05
Calf's liver	0.12	0.033
Calf's spleen	0.16	0.046

[1] Minkowski: "Archiv. für experimentelle Path. und Pharm.," 1886, Bd. xxi, p. 41.

[2] Steudel: "Zeitschrift für physiologische Chemie," 1903, Bd. xxxix, p. 136.

[3] Burian: "Zeitschrift für physiologische Chemie," 1905, Bd. xliii, p. 532.

[4] Burian and Schur: "Pfluger's Archiv," 1900, Bd. lxxx, p. 308.

To obtain the amount of endogenous uric acid present in the urine, if it were produced by the destruction of nucleoproteins, it would be necessary to destroy completely a quantity of nucleoprotein equal to that contained in more than 100 grams of liver. It does not seem possible that nuclein destruction or nuclein metabolism could reach this extent.

The experiments of Burian[1] consisted in perfusing dog's muscles with blood free from uric acid. He noticed that after the perfusion of such blood through the muscles, uric acid was constantly found in it. If the muscle was caused to contract during the perfusion, a very considerable increase in the quantity of the purin bases was found in the blood and there was an increase in the quantity of these bases found in the muscles themselves.

Burian concludes that in the resting muscle there is a constant production of hypoxanthin which is converted into uric acid through the activity of the xanthin oxidase. In the active muscle there is a greater production of hypoxanthin which is not completely oxidized on account of a local oxygen deficiency.

It had been found by many previous observers that exercise has no effect on the purin excretion in the urine of twenty-four hours in man. Burian, however, finds a large increase in the purin elimination for an hour or two after severe muscular exercise, and this is followed by a compensatory reduction in the output during those subsequent hours which represent the interval of weariness in the muscle.

These observations were confirmed by the work of Rockwood,[2] who saw that the purin excretion was less during the night than during the day, and by the work of Pfeil,[3] who found a constant morning rise in the output of purins in human urine.

These facts confirm Burian's contention that the most general source of endogenous purins is a constant production of hypoxanthin in muscle, a production which varies with the

[1] Burian: *Loc. cit.* [2] Rockwood: *Loc. cit.*

[3] Pfeil: "Zeitschrift für physiologische Chemie," 1904, Bd. xl, p. 1.

individual and is possibly proportional to the mass of his musculature. Comparable to this is the constant production of creatinin (p. 138). Hypoxanthin is oxidized to uric acid in the muscle, and uric acid, if carried to the liver, which is certainly the principal organ for its destruction, may there be oxidized. Such of the purin bases as escape oxidation may be excreted by the blood flowing through the kidney, even as uric acid is excreted under the same circumstances.

Siven[1] does not believe that muscular work appreciably raises the production of endogenous purins. He thinks that the reduction in purin elimination during the night time is due to general inactivity of all the tissues, and shows that when an evening meal containing much protein is taken and the kidney is made thereby to functionate during the night, then the purin elimination is increased. Burian's discovery of increased elimination during work was perhaps due to the fact that the work was accomplished during the morning hours, when an increased elimination due to purins retained during the night would normally occur.

Mendel and Brown[2] have determined the hourly excretion of uric acid as influenced by the ingestion of meat, liver, and other animal tissues. The increase in the eliminated uric acid is very marked and reaches a maximum two or three hours after the ingestion of these animal tissues. Thus after the ingestion of 600 grams of chopped meat the uric acid elimination, which had been 19 milligrams, rose during the following three hourly periods to 28, 88, and 98 milligrams and then fell in successive hours to 79, 73, 51, 36, 25, and 22 milligrams. It will be seen later that such curves of exogenous uric acid excretion do not occur in the gouty patient in whom there is uric acid retention (see p. 354).

Just as the whole trouble in diabetes turns upon the in-

[1] Siven: Abstract in "Zentralblatt für Stoffwechsel," 1906, Bd. i, p. 81.

[2] Mendel and Brown: "Journal of the American Medical Association," 1907, vol. xlix, p. 896.

ability of the organism to destroy sugar, so the symptoms manifested in gout are dependent upon the deposit of acid urate of sodium in certain localities. One of the earliest descriptions of gout comes from Sydenham, who suffered for forty years from the disease and published an extended account of it in 1683. It was Garrod[1] who first established the fact that uric acid was present in the blood of gouty persons. He believed that this excess of urate was the cause of gout, the excess being deposited from the blood in the joints in the form of crystals. The problem of metabolism in gout is a problem of the factors entering into the cause of this deposit of urate. The general metabolism, exclusive of the purin factor, is exactly the same as in health. Magnus-Levy[2] proved that the oxygen absorption and carbon dioxid elimination is the same in gout as in health. The cause of the trouble must be sought elsewhere than in a reduced general oxidation power of the tissues.

Clinical experience teaches that the predisposing causes are excessive eating, little muscular exercise, the abuse of alcoholic beverages, and lead-poisoning.

Beebe[3] has administered alcohol in various forms to a normal individual. He finds that even large doses have no effect on the hourly excretion of uric acid in a fasting man. The endogenous purin metabolism is therefore unchanged by the ingestion of alcohol. It is important to know that alcohol is apparently without effect upon such part of the purins as may be directly derived from cell metabolism. On the other hand, when Beebe gave alcohol with nuclein-containing food, the uric acid elimination rose markedly. Further investigation of this subject by Landau[4] has revealed the fact that the influence of alcohol is different in different individuals, and that usually there is a slight increase in the output of endogenous purins after

[1] Garrod: "The Nature and Treatment of Gout," 1859.

[2] Magnus-Levy: "Berliner klinische Wochenschrift," 1896, No. xix, p. 416.

[3] Beebe: "American Journal of Physiology," 1904, vol. xii, p. 13.

[4] Landau: "Deutsches Archiv für klinische Medizin," 1909, Bd. xcv, p. 280.

taking alcohol. Landau also found that there was always a diminution of exogenous purins in the urine as a result of alcohol ingestion. Thus while 48.4 per cent. of hypoxanthin given in a diet free from purins was eliminated in the urine as uric acid on a normal day, only 38.2 per cent. was excreted as uric acid when alcohol was added to the diet. This is interpreted as indicating that alcohol causes a retention of uric acid within the organism.

Pollack[1] has shown that in chronic alcoholics the retention of ingested purins is favored.

Minkowski,[2] with a master hand, summarizes modern knowledge concerning gout as follows:

1. The deposit of urate in the tissues is the first change which takes place in the formation of the specific gouty nodules. These tissues are not necrotic, as taught by Ebstein.

2. The tissue changes in the vicinity of the gouty nodules are in part due to mechanical, in part to chemical or osmotic action, caused by the precipitated urates.

3. The acute inflammation in gout, as observed during the attack, is produced in the vicinity of the urate deposits through some unknown cause. Traumatic, toxic, or infectious elements appear to be collectively active in this regard. The attack probably constitutes the reaction of the organism to rid itself of uric acid, an effect which is only partly realized.

4. An accumulation of uric acid in the blood is a constant accompaniment of gout.

5. The increased quantity of uric acid in the blood must not be considered as the cause of the precipitation of urates in the gouty nodules. There must be certain local influences which favor the deposit of urates; for Klemperer has shown that the blood of gouty patients may dissolve much more uric acid than is actually present in it; and again, the blood in leukemia may

[1] Pollack: "Deutsches Archiv für klin Med.," 1906, Bd. lxxxviii, p. 224.

[2] Minkowski: von Leyden's "Handbuch der Ernährungstherapie," 1904, Bd. ii, p. 277.

contain as much uric acid as in gout, without there being any indication of a deposit of urate.

6. The uric acid elimination is the same in the gouty as in the normal person, except at the time of the attack. Before the attack there is retention, but during and after the attack an increased excretion of uric acid in the urine.

7. The accumulation of uric acid in the blood is not due to a diminished oxidation of uric acid, but rather to a diminution in the quantity excreted in the urine.

8. It is not certain that the lessened excretion of uric acid is due to a disturbance of renal function. Very likely it depends upon the presence of uric acid in some abnormal chemical union. This abnormal substance may be with difficulty eliminated in the urine, but may lend itself readily to the formation of tophi (p. 338).

9. The ultimate cause of the unusual behavior of uric acid in gout is probably an abnormal metabolism within the nuclei of the cells, where the nucleic acid content is the means of solution and conveyance not only of the purin bases but also of uric acid.

The opinions of other modern workers vary somewhat from those of Minkowski, as appears in the following:

Almagia,[1] in Hofmeister's laboratory, has performed some interesting experiments and concludes that the older view of Garrod is correct,—that is, that an excess of urates in the blood is the cause of gout. Almagia finds that thin strips of cartilage suspended in dilute neutral solutions of sodium urate absorb the salt, do not destroy it, but cause it to be deposited in fine crystals within the cartilage. He furthermore injected five to seven grams of uric acid into the peritoneal cavity of rabbits, a dose which usually killed them. On testing the liver, spleen, muscles, and lungs with the murexid test for uric acid, negative results were obtained, whereas cartilage gave a positive reaction indicating the presence of urates. Almagia concludes that

[1] Almagia: "Hofmeister's Beiträge," 1905, Bd. vii, p. 466.

the deposit of urates in the cartilage of a gouty patient is but the result of a temporary or permanent increase in the uric acid content of the blood.

Still, in leukemia, where there must be a large destruction of nucleoprotein, as evidenced by a report concerning a patient who eliminated 12 grams of uric acid during the last forty hours of life, there is no gout.[1]

Magnus-Levy,[2] Vogt,[3] and Reach[4] were the first to discover that the administration of glands rich in nucleoprotein, such as thymus and pancreas, to gouty persons, did not cause as large an excretion of uric acid in the urine as when the same amounts of these materials were given to normal individuals.

The work of Soetbeer[5] is of the best modern character, and illustrates the retention of uric acid in gout. Soetbeer compared the excretion of uric acid by gouty people during three-hour intervals with that of normal individuals, as observed by Pfeil (p. 349). In one case of long-standing gout, of light character and with long intervals between the attacks, there was little variation from the normal in the uric acid excretion. In another case of gout, a patient who was examined between the attacks showed no increase in uric acid output after changing from a purin-free diet to one containing 320 grams of meat, and showed only a slight increase in elimination after 640 grams of meat were given. These results were obtained six weeks after the last attack and at a time when the patient was entirely free from pain. In still another case 350 grams of meat were given during the attack to a gouty patient who had no fever and whose urine was free from albumin and sugar. The results were as follows:

[1] Magnus-Levy: "Virchow's Archiv," 1898, Bd. clii, p. 107.
[2] Magnus-Levy: "Zeitschr. für klin. Med.," 1899, Bd. xxxvi, p. 414.
[3] Vogt: "Deutsches Arch. für klin. Med.," 1901, Bd. lxxi, p. 21.
[4] Reach: "Münchener med. Wochenschr.," 1902, Bd. xlix, p. 1215.
[5] Soetbeer: "Zeitschrift für physiologische Chemie," 1904, Bd. xl, p. 54.

	Uric Acid in Grams.
Diet free from purins	0.276
Diet free from purins	0.328
Diet + 350 grams meat	0.316
" " " "	0.270
" " " "	0.255

In this experiment even during the days of purin-free diet there was no "morning rise" noted as a normal incident by Pfeil. The hourly uric acid excretion was very even. The kidney was apparently removing uric acid up to the limit of its capacity.

Linser[1] tells how a gouty individual suffering from eczema was treated with the Roentgen rays. Although the person was on a purin-free diet, the treatment invariably brought on an attack of gout, on account of the increased production of uric acid within the body which normally follows such treatment.

Von Noorden and Schliep[2] suggest that gouty patients be tested for their "tolerance" for purin bodies just as diabetics are tested for their tolerance for carbohydrates. Four hundred grams of meat contain 0.24 gram of purin nitrogen, of which in the normal person one-half is oxidized and one-half eliminated in the urine—0.24 gram N = 0.72 gram uric acid. A patient was put on a purin-diet free; was given 400 grams of meat, then put on a purin-free diet again, and afterwards was tested with 200 grams of meat. The results were as follows:

Day.	Diet.	Uric Acid in Grams.
4	Purin-free	0.462
5	" " + 400 g. meat	0.522
6	" " + 400 g. meat	0.544
7	" "	0.539
8	" "	0.528
9	" "	0.458
10	" " + 200 g. meat	0.549
11	" " + 200 g. meat	0.655
12	" "	0.647
13	" "	0.499
14	" "	0.433

[1] Linser: "Therapie der Gegenwart," 1908, No. 4.

[2] Von Noorden and Schliep: "Berliner klinische Wochenschrift," 1905, Bd. xlii, p. 1297.

The authors conclude that while the increased uric acid output after giving 400 grams of meat is not what it would be normally, yet after giving 200 grams the quantity of additional uric acid (which should amount to 0.18 gram) is fully eliminated. Hence this patient had a tolerance for the purins in 200 grams of meat.

Dietetic rules for gouty sufferers are intended to combat the fundamental anomalies of the metabolism. The organism must not be overloaded with uric acid. Minkowski's rules[1] for treatment of gout may be thus abstracted: Sweetbreads, liver, and kidney are to be strictly excluded from the diet since they contain purin bases in large quantity. Meat is to be taken in moderation only. Wine should be taken sparingly or not at all, and beer rigidly excluded on account of the nuclein in yeast. Cathartics may be given to rid the intestine of purin bodies excreted into the intestinal canal, and water-drinking, which promotes a larger flow of urine and increased uric acid elimination, is strongly to be commended. The diet for a gouty patient should contain each day 100 or 120 grams of protein, 80 or 100 grams of fat, and 250 or 300 grams of carbohydrates (2200 to 2600 calories). This should not include more than from 200 to 250 grams of meat per day. Indigestible cakes, pies, rich foods, and heavy salads should be forbidden. Moderation and self-control are the watchwords for the gouty sufferer.

It is impossible to increase the oxidation of uric acid, and no treatment now known increases its solubility. Minkowski hopes that some organic compound may be discovered which will accomplish this purpose. He believes the relief given by preparations of the salicylate group is afforded only through their stopping pain and promoting perspiration.

Bearing the facts of the above discussion in mind, the reader will comprehend that present-day doctrines concerning metabolism in gout may shortly become entirely obsolete through new and far-reaching discoveries.

[1] Minkowski: "Deutsche medizinische Wochenschrift," 1905, Bd. xxxi, p. 409.

CHAPTER XV.

THEORY OF METABOLISM.

There has been a difference of opinion as to whether the food substances must first become vital integrants of the living cell, or whether the non-living food materials are metabolized without ever becoming a constituent part of the living protoplasm.

Pflüger held the former view,—that incorporation of nutritive matter with the living substance is essential to its metabolism. He conceived that living protein may contain the labile cyanogen group in contrast with dead protein which contains the amino group. He illustrated this by Wöhler's classic experiment of the easy conversion of ammonium cyanate into urea:

$$NH_4OCN = (H_2N)_2CO$$

Voit's theory was that the living protein is comparatively stable and that food protein which becomes the circulating protein of the blood is carried to the cells and promptly metabolized. The other foodstuffs are also burned without first entering into the composition of the cell.

A mass of living cells composing the substance of a warm-blooded animal has the same requirement of energy as any similar mass of living cells composing the substance of any other animal of the same size and shape.

The uniformity of the energy requirement is illustrated by the fact that the number of calories given off during the twenty-four hours by one square meter of surface, in various animals and in man in the condition of starvation, is the same.

Even in pathological conditions a remarkable constancy of total heat production is apparent. Thus, in such typical dis-

turbances as anemia, diabetes, gout, and obesity, the general laws governing the output of carbon dioxid, the absorption of oxygen, and the production of heat are found to be the same as in health. Also after castration the metabolism is unchanged, except as it may be influenced by increased indolence. In fever the metabolism and heat production increase, and this to a large extent on account of the warming of the cells. In exophthalmic goiter there is certainly an increase in metabolism, due to the stimulus of an excessive production of iodothyrin in the thyroid gland, while in myxedema the absence of the same substance causes a considerable reduction in the metabolism. These changes are probably due to alterations in the irritability of the nervous system. Drugs may influence the course of metabolism, iodothyrin increasing it and morphin profoundly diminishing it, but on the whole the most striking fact is not the variability, but rather the uniformity, of the processes concerned in the maintenance of life.

Within recent years the work of Kossel, Fischer, Hofmeister, Osborne, Abderhalden and Levene has given a more definite conception of the composition of protein than was before possible. There is every indication that the protein molecule consists fundamentally of groups of amino-fatty acids banded together. Proteins vary with the integral components of their chemical chains. It has long been known that the end-products of tryptic digestion include such substances, but Kutscher first showed that continued tryptic digestion resulted in the almost complete transformation of protein into these amino-acids. Cohnheim discovered erepsin, an enzyme derived from the intestinal wall, which rapidly converts albumoses into these substances.

Protein metabolism in plants and animals occurs in striking similarity to the changes brought about by enzymes and hydrolytic agents acting on protein outside of the tissues. Thus in the germinating seed Schultze[1] finds that asparagin, leucin,

[1] Schultze and Castoro: "Zeitschr. f. physiol. Chemie," 1904, Bd. xliii, p. 170.

tyrosin, histidin, arginin, and lysin arise from the metabolism of protein.

All forms of protein decomposition follow, therefore, the pathway of cleavage into amino-acids. This all indicates a wonderful biological kinship.

The metabolic history of many of these substances has already been set forth in the preceding chapters, and it is here unnecessary to recapitulate.

The quantity of the combustion depends on the power of the cells to metabolize (Voit). In the resting state this metabolic power of the cells is influenced by the "law of skin area" (Rubner). Temperature (cooling or warming) and nerve excitation (muscle work, chemical regulation) affect the power of the cells to metabolize, perhaps through a variation in the capability of oscillation of the particles, an effect which is in turn maintained at the expense of the energy derived from metabolism. Living protoplasm metabolizes in accord with its necessities at the time, and never more. A large supply of nutrient materials will not increase cell metabolism. If food be ingested above the requirement for the organism, any excess will be retained in the body (unless it has passed out undigested). The kind of metabolism depends upon the constitution of the fluid feeding the cells, whether proteins, carbohydrates, or fats have been ingested. The reason for the metabolism lies unknown within the cells. Liebig conceived the cause to be the swinging motion of the small constituent particles of the cells themselves.

Rubner[1] gives the following theory of metabolism. The nature of the processes which take place in living protoplasm is not known. High-sounding names which have been used in this connection are only a cloak for ignorance. The colloidal condition of the protoplasm of the cells in both warm and cold blooded animals is nearly identical. All cells, however, are not similar in constitution, since some bacteria are killed at

[1] Rubner: "Archiv für Hygiene," 1908, Bd. lxvi, p. 15.

30° while others thrive at 60°. This latter variety must synthesize proteins which are not coagulable at the higher temperature. One may imagine the mechanism of the energy metabolism to be somewhat as follows. The whole mass of the protoplasm cannot be continually employed in the production of energy but only certain parts of it. These parts, by virtue of the characteristic vibration of their molecules, possess the power to attract and break up contiguous food radicles. Such *affinities* must be *specific*. It is necessary to consider two fundamental types of cell affinities: (1) for carbohydrates and (2) for fat—neglecting those for alcohol, glycerin, etc. One is led to this because it is known that in diabetes the affinity for carbohydrate is lost while that for fat remains. When the necessity for increased mechanical effect arises, the amplitude of the vibrations, or, in other words, the strength of the affinities, is increased by means of nerve stimuli. It is immaterial to the life of protoplasm which of the two affinities is used. If the carbohydrate type of cell affinity is active, that for fat becomes inactive and *vice versa*. If the carbohydrate type is annihilated, as in diabetes, then the fat type may alone provide for the energy production. The affinities of the vibrating molecules may be considered as acting somewhat in the same way as enzymes, but this similarity is limited to the primary attack upon the food radicles. The approach of the nutrient radicles within the range of the affinities is accompanied by atomic changes in the food particles and possibly by the immediate entrance of oxygen. How the oxygen enters into the complex is not definitely known, but the important consideration relates to the liberation of energy. The sequence of the atomic changes and the entrance of oxygen must be so ordered that at the moment of the breaking up the nutrient radicles, mechanical work is accomplished upon the living protoplasm, work which can be expended upon neighboring parts of the protoplasm and which for the time renders the affinities inactive. It is entirely a matter of indifference whether the result is obtained from carbohydrate or from fat, for the law

of isodynamic equivalents asserts that the requirement of energy may be satisfied either by carbohydrates or by fat. The living protoplasm acquires energy at the moment of the break-down of the foodstuffs. This acquired swinging motion of the molecules gradually subsides with the evolution of heat, and the original condition in which the affinities were active returns and again more food radicles are attacked. This theory of metabolism represents Rubner's idea of the method by which the energy of the food is transmitted to the living protoplasm in response to the demand for energy for the maintenance of life. Besides this a number of cleavages and other changes in chemical constitution occur which also either evolve or absorb heat. These are purely thermo-chemical processes and do not furnish the body with energy in the sense just described.

Each ingested foodstuff exerts a specific dynamic action (Rubner). At a temperature of 33° the ingestion of the starvation requirement of energy in the form of fat increases the requirement for energy 10 per cent., carbohydrate raises it 5 per cent., protein 30 per cent. In other words, in the case of meat, in order to obtain calorific equilibrium about 140 calories must be ingested instead of 100, if that represents the starvation requirement. Rubner[1] explains that the cells of the body do not require more energy after meat ingestion than in starvation, but that the heat produced by a preliminary cleavage of protein into dextrose on the one hand, and into a nitrogen-containing rest on the other, while yielding heat to the body does not furnish the actual energy for the vital activities of the protoplasm. This is furnished principally by the dextrose derived from the protein. Although it is necessary to abandon the older theory which pronounces glycogen (or dextrose) a direct cleavage product of protein, still the explanation of Rubner remains tenable if interpreted in a newer light. If the energy requirement of the cell remains constant at 100, even after the ingestion of 140 calories of protein, then 71.4 per cent. of the total heat value of the protein is the quantity actually used for the vital processes.

[1] Rubner: "Gesetze des Energieverbrauchs," 1902, p. 380.

Since it has been shown in the writer's laboratory that meat protein yields 58 per cent. of dextrose in metabolism, it may be calculated that 52.5 per cent. of the total energy of protein may be available for the cells in the form of sugar. A balance of 19 per cent. must be obtained from other compounds, while 28.5 per cent. of the total heat value is wasted as heat without ever having been brought into the service of the life processes of the cells. (See p. 163.)

The constancy of the energy requirement in metabolism makes difficult the explanation of the action of the various ferments found in the body. These are of three varieties: hydrolytic, synthetic, and oxidizing, but these, from the very principles of our knowledge, must be subservient to the requirement of the living cells, and not themselves masters of the situation, as, for example, they become in the autolysis of dead tissue. It seems to be the requirement of the mechanism of cell activity which determines metabolism, and not primarily the action of enzymes, whose influence appears to be only intermediary.

Friedenthal[1] shows that protein, colloidal carbohydrates, fats, and soaps are not oxidizable in the cellular fluids without previous hydrolytic cleavage. After hydrolysis, however, the oxidases may effect an oxidation of the smaller molecules. The necessity of the hydrolytic ferment is also seen in the non-combustion of dextrose after the extirpation of the pancreas, the organ by which the ferment is supplied. Oxygen and the oxidases are present in ample quantity, but the sugar is not burned unless it be broken by its specific ferment. In the meantime the cell avails itself of a compensatory energy supply from other sources. Metabolism depends therefore upon a definite law of utilization of energy equivalents.

However clearly formulated the laws of metabolism may be, and many of them are as fixed and definite as are any laws of physics and chemistry, still the primary cause of metabolism remains a hidden secret of the living bioplasm.

[1] Friedenthal: Verhandlungen der Berliner physiologischen Gesellschaft, "Archiv für Physiologie," 1904, p. 371.

APPENDIX.

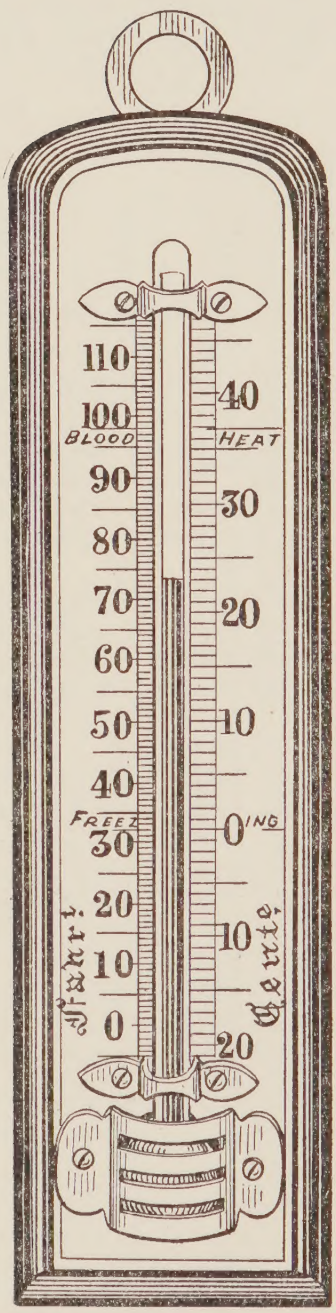


Fig. 13.—Thermometer showing comparison of Fahrenheit and Centigrade scales.

CONVENIENT COMPARISONS OF METRIC AND AVOIRDUPOIS WEIGHTS.

1 kilogram = 2.2046 pounds
1 pound = 453.6 grams
1 ounce = 28.3 grams
1 liter = 61.027 cubic inches = 1.7608 pints
1 gram-calorie = 0.425 kilogram-meters of mechanical energy.

THE CHEMICAL COMPOSITION OF NORMAL URINES ON PURIN-FREE DIETS. (After Folin, see p. 138.)

	Person.						
	E. S. A.		H. B. H.				
	June.		March.			July.	
	29th	30th	8th	9th	10th	13th	20th
Total N in grams	14.6	15.8	15.9	15.5	15.0	16.8	3.6
Urea N	12.6	13.9	13.5	13.4	12.9	14.7	2.2
Ammonia N	0.54	0.54	0.41	0.41	0.43	0.49	0.42
Creatinin N	0.39	0.43	0.70	0.64	0.69	0.58	0.60
Uric Acid N	0.15	0.11	0.26	0.23	0.27	0.18	0.09
Undetermined N	0.96	0.88	1.06	0.79	0.68	0.85	0.27
Total SO_3 in grams	3.02	2.94	3.03	2.49	2.19	3.64	0.76
Inorganic SO_3	2.56	2.58	2.48	2.05	1.74	3.27	0.46
Ethereal SO_3	0.26	0.22	0.20	0.18	0.19	0.19	0.10
Neutral SO_3	0.20	0.14	0.35	0.26	0.26	0.18	0.20
In per cent. of total N:							
Urea N	86.0	87.7	84.7	86.4	86.2	87.5	61.7
Ammonia N	3.6	3.3	2.6	2.7	2.9	3.0	11.3
Creatinin N	2.7	2.7	4.4	4.1	4.6	3.6	17.2
Uric Acid N	1.0	0.7	1.6	1.7	1.8	1.05	2.5
Undetermined N	6.6	5.6	6.7	5.1	4.4	4.85	7.3
In per cent. of total SO_3							
Inorganic SO_3	84.7	87.7	81.8	82.0	79.4	90.0	60.5
Ethereal SO_3	8.6	7.4	6.6	7.2	8.6	5.2	13.2
Neutral SO_3	6.7	4.9	11.6	10.8	12.0	4.8	26.5

TABLE SHOWING THE COST OF PROTEIN AND ENERGY

As Furnished by a Number of Common Food Materials, at Prices Current in the Eastern Part of the United States.

Compiled by Langworthy, U. S. Department of Agriculture, 1905, in Farmers' Bulletin, No. 85, p. 19.

(1 pound = 453.6 grams.)

Kind of Food Material.	Price per Pound.	Cost of 1 Pound Protein.	Cost of 1000 Calories Energy.	Amounts for 10 Cents.		
				Total Weight of Food Material.	Protein.	Energy.
	Cents.	*Dollars.*	*Cents.*	*Lbs.*	*Lb.*	*Calories.*
Codfish, whole, fresh	10	0.90	48	1.000	0.111	209
Codfish, steaks	12	71	36	.833	.142	274
Bluefish	12	1.20	58	.833	.083	172
Halibut	18	1.18	40	.556	.085	253
Codfish, salt	7	.44	23	1.429	.229	437
Mackeral, salt	10	.61	10	1.000	.163	998
Salmon, canned	12	.62	18	.833	.162	547
Oysters (solids, 30 cents quart)	15	2.50	68	.667	.040	147
Oysters (solids, 60 cents quart)	30	5.00	136	.333	.020	74
Lobster	18	3.05	129	.556	.033	77
Beef, sirloin steak	25	1.52	26	.400	.066	380
Beef, sirloin steak	20	1.21	21	.500	.083	475
Beef, round	14	.74	16	.714	.136	615
Beef, stew meat	5	.38	5	2.000	.266	1,862
Beef, dried, chipped	25	.95	33	.400	.106	303
Mutton chops, loin	20	1.48	14	.500	.068	694
Mutton, leg	22	1.46	25	.454	.069	394
Pork, roast, loin	12	.90	10	.833	.112	1,016
Pork, smoked ham	22	1.55	14	.454	.064	729
Milk (7 cents quart)	3	1.06	11	2.857	.094	891
Milk (6 cents quart)	3	.91	10	3.333	.110	1,040
Wheat flour	3	.26	2	3.333	.380	5,363
Corn meal	2	.22	1	5.000	.460	8,055
Potatoes (90 cents bushel)	1½	.83	5	6.667	.120	2,020
Potatoes (45 cents bushel)	¾	.42	2	13.333	.240	4,040
Cabbage	2½	1.79	21	4.000	.056	484
Corn, canned	10	3.57	23	1.000	.028	444
Apples	1½	5.00	7	6.667	.020	1,420
Bananas	7	8.75	24	1.429	.011	414
Strawberries	7	7.78	42	1.429	.013	240

A more extensive compilation which permits not only the calculation of the nutritive value of the particular edible food but also of the approximate weight of inedible waste entailed in the direct purchase of the material in the market, is as follows:

COMPOSITION OF ORDINARY FOOD MATERIALS

ACCORDING TO ATWATER AND BRYANT.

Report of the Storrs Agricultural Experiment Station, 1899, p. 113, somewhat abridged.

KIND OF FOOD MATERIAL.	Inedible Refuse of Purchased Material.	EDIBLE PORTION.						
		Water	Unavailable Nutrients.	AVAILABLE NUTRIENTS.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel value per lb. = 453.6 Grams.
ANIMAL FOODS. *Beef (fresh).*	%	%	%	%	%	%	%	Calories.
Brisket	23.3	54.6	2.1	15.3	27.1	..	.7	1475
Chuck	16.3	62.7	1.8	17.9	17.1	..	.7	1095
Flank	10.2	60.2	1.9	18.3	19.9	..	.7	1225
Loin, lean	13.1	67.0	1.2	19.1	12.1	..	1.0	900
Loin, medium	13.3	60.6	1.8	17.9	19.2	..	.8	1185
Loin, fat	10.2	54.7	1.9	17.0	26.2	..	.9	1470
Neck	27.6	63.4	1.6	19.5	15.7	..	.7	1065
Plate	16.5	54.4	2.2	16.0	27.6	..	.6	1510
Ribs	20.8	55.5	2.0	17.0	25.3	..	.7	1430
Round, lean	8.1	70.0	1.0	20.7	7.5	..	1.1	735
Round, medium	7.2	65.5	1.6	19.7	12.9	..	.8	950
Round, fat	12.0	60.4	1.6	18.9	18.5	..	1.0	1175
Round, second cut	19.5	69.8	1.3	19.8	8.2	..	.8	750
Rump	20.7	56.7	2.0	16.9	24.2	..	.7	1380
Fore shank	36.9	67.9	1.4	19.8	11.0	..	.7	865
Tongue	26.5	70.8	1.3	18.3	8.7	..	.8	740
Shoulder and clod	16.4	68.3	1.5	19.0	10.7	..	.8	840
Fore quarter	18.7	60.4	1.8	17.4	20.3	..	.7	1220
Hind quarter	15.7	59.8	1.8	17.8	20.5	..	.7	1240
Side, lean	19.5	67.2	1.3	18.7	12.5	..	.9	910
Side, medium	17.4	59.7	1.8	17.6	20.9	..	.7	1250
Side, fat	13.2	47.8	2.5	15.7	34.6	..	.5	1805
Liver	7.0	71.2	1.2	20.4	4.3	1.7	1.2	620
Suet (unrendered tallow)	..	13.7	4.3	4.6	77.7	..	.2	3440
Hind Shank	53.9	67.8	1.4	20.3	10.9	..	.7	875
Beef (preserved and cooked).								
Dried and smoked	4.7	54.3	3.5	29.1	6.2	..	6.8	850
Brisket, corned	21.4	50.9	3.2	17.8	23.5	..	4.2	1370
Flank, corned	12.1	49.9	2.7	14.2	31.4	..	2.2	1635

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
		Water.	Unavailable Nutrients.	Available Nutrients.				
				Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Animal Foods. (*Beef, preserved and cooked*).	%	%	%	%	%	%	%	Calories.
Plate, corned	14.5	40.1	3.7	13.3	39.8	..	3.5	1980
Rump, corned	6.0	58.1	2.2	14.8	22.1	..	2.8	1250
Canned, boiled	..	51.8	2.2	24.7	21.4	..	1.0	1415
Canned, corned	..	51.8	2.7	25.5	17.8	..	3.0	1275
Boiled beef (cut not given)	..	38.1	2.7	25.4	33.2	..	.7	1930
Roast, cooked	..	48.2	2.4	21.6	27.2	..	1.0	1410
Loin steak, cooked	..	54.8	2.0	22.8	19.4	..	.9	1290
Tripe, pickled	..	86.5	.6	11.3	1.1	..	.2	275
Veal (fresh).								
Breast	21.3	66.0	1.5	18.9	13.3	..	.8	950
Chuck	18.9	73.0	1.1	19.1	6.2	..	.8	650
Cutlets (round)	3.4	70.7	1.3	19.7	7.3	..	.8	710
Flank	..	68.9	1.3	19.9	9.9	..	.8	825
Leg	14.2	70.0	1.3	19.6	8.6	..	.9	760
Loin	16.5	69.0	1.3	19.3	10.3	..	.8	830
Neck	31.5	72.6	1.1	19.7	6.6	..	.8	680
Rib	24.3	72.7	1.2	20.1	5.8	..	.8	650
Shank	62.7	74.5	1.0	20.1	4.4	..	.8	590
Fore quarter	24.5	71.7	1.2	19.4	7.6	..	.7	715
Hind quarter	20.7	70.9	1.2	20.1	7.9	..	.8	740
Side	22.6	71.3	1.2	19.6	7.7	..	.8	725
Liver	..	73.0	.9	9.7	5.0	..	1.0	410
Lamb (fresh).								
Breast or chuck	19.1	56.2	2.0	18.5	22.4	..	.8	1335
Leg	17.4	63.9	1.7	18.6	15.7	..	.8	1050
Loin	14.8	53.1	2.2	18.1	26.9	..	.8	1520
Neck	17.7	56.7	1.9	17.2	23.6	..	.8	1360
Shoulder	20.3	51.8	2.2	17.6	28.2	..	.8	1565
Fore quarter	18.8	55.1	2.0	17.8	24.5	..	.8	1410
Hind quarter	15.7	60.9	1.8	19.0	18.1	..	.8	1160
Side	19.3	58.2	2.0	17.1	21.9	..	.8	1285
Lamb (cooked).								
Chops, broiled	13.5	47.6	2.5	21.0	28.4	..	1.0	1640
Leg, roast	..	67.1	1.4	19.1	12.1	..	.6	905
Mutton (fresh).								
Chuck	21.3	50.9	2.4	14.6	31.9	..	.7	1665
Flank	9.9	46.2	2.6	14.7	36.4	..	.5	1860

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Animal Foods. *Mutton (fresh)*	%	%	%	%	%	%	%	Calories.
Leg	18.4	62.8	1.7	17.9	17.1	..	.8	1095
Loin	16.0	50.2	2.4	1.55	31.4	..	.6	1660
Neck	27.4	58.1	2.0	16.4	23.4	..	.7	1335
Shoulder	22.5	61.9	1.7	17.2	18.9	..	.7	1160
Fore quarter	21.2	52.9	2.2	15.1	29.4	..	.7	1570
Hind quarter	17.2	54.8	2.1	16.2	26.7	..	.6	1475
Side	18.1	54.2	2.1	15.8	27.5	..	.7	1500
Mutton (cooked and canned).								
Leg, roast	..	50.9	2.1	24.3	21.5	..	.9	1410
Corned, canned	..	45.8	3.0	27.9	21.7	..	3.2	1495
Tongue, canned	..	47.6	3.1	23.7	22.8	..	3.6	1045
Pork (fresh).								
Chuck, ribs and shoulder.	18.1	51.1	2.3	16.8	29.5	..	.7	1605
Flank	18.0	59.0	1.9	17.9	21.1	..	.8	1265
Loin, chops	19.7	52.0	2.2	16.1	28.6	..	.8	1555
Ham	10.7	53.9	2.1	14.8	27.5	..	.6	1480
Shoulder	12.4	51.2	2.3	12.9	32.5	..	.6	1660
Side	11.5	34.4	3.2	8.8	52.5	..	.4	2440
Pork (pickled, salted and smoked).								
Bacon	7.7	18.8	4.8	9.6	64.0	..	3.3	2950
Ham	13.6	40.3	3.6	15.8	36.9	..	3.6	1905
Shoulder	18.2	45.0	3.8	15.4	30.9	..	5.0	1640
Salt, lean ends	11.2	19.9	5.1	8.1	63.7	..	4.3	2905
Salt, fat	..	7.9	5.4	1.8	81.9	..	2.9	3565
Pigs' feet, pickled	35.5	68.2	1.4	15.8	14.1	..	.7	920
Pork (cooked).								
Ribs, cooked	..	33.6	3.1	24.1	35.7	..	1.7	2020
Steak, cooked	..	33.2	3.3	19.3	43.1	..	1.1	2245
Sausage.								
Bologna	3.3	60.0	2.4	18.1	16.7	0.3	2.8	1085
Frankfort	..	57.2	2.3	19.0	17.7	1.1	2.6	1160
Pork	..	39.8	3.1	12.6	42.0	1.1	1.7	2080
Poultry and game (fresh).								
Chicken, broilers	41.6	74.8	1.0	20.9	2.4	..	.8	520
Fowl	25.9	63.7	1.6	18.7	15.5	..	.8	1040
Goose	17.6	46.7	2.5	15.8	34.4	..	.6	1800
Turkey	22.7	55.5	1.9	20.5	21.8	..	.8	853

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Animal Foods.	%	%	%	%	%	%	%	Calories.
Poultry and game (cooked and canned).								
Capon	10.4	59.9	1.7	26.2	10.9	..	1.0	995
Turkey, roast	..	67.5	1.3	17.1	10.9	.8	2.4	855
Plover, roast, canned	..	57.7	1.7	21.7	9.7	1.6	7.6	985
Quail, canned	..	66.9	1.6	21.1	7.6	1.1	1.7	780
Fish (fresh).								
Bass, black, whole	54.8	76.7	1.0	20.0	1.6	..	.9	470
Bluefish	48.6	78.5	1.0	18.8	1.1	..	1.0	420
Codfish, dressed	29.9	58.5	.5	10.8	.2	..	.6	225
Cod steaks	9.2	79.7	.9	18.1	.5	..	.9	385
Flounder, whole	61.5	84.2	.7	13.8	.6	..	1.0	300
Haddock	51.0	81.7	.8	16.7	.3	..	.9	345
Halibut steak	17.7	75.4	1.1	18.0	4.9	..	.8	570
Lake trout	48.5	70.8	1.3	17.3	9.8	..	.9	765
Mackerel	44.7	73.4	1.3	18.1	6.7	..	.9	650
Weakfish	51.9	79.0	.9	17.3	2.3	..	.9	445
Whitefish, whole	53.5	69.8	1.4	22.2	6.2	..	1.2	710
Shell fish (fresh).								
Long clams, in shell	41.9	85.8	1.0	8.3	.9	2.0	2.0	240
Round clams, in shell	67.5	86.2	.9	6.3	.4	4.2	2.0	215
Oysters, in shell	81.4	86.9	.8	6.0	1.1	3.7	1.5	235
Oysters, solids	..	88.3	.6	5.8	1.2	3.3	.8	225
Clams, round, solids	..	80.8	1.0	10.3	1.0	5.2	1.7	340
Crabs, hard shells	52.4	77.1	1.4	16.1	1.9	1.2	2.3	425
Lobster	61.7	79.2	1.1	15.9	1.7	.4	1.7	400
Fish (preserved and canned).								
Cod, salt	24.9	53.5	6.8	20.9	.3	..	18.5	430
Cod, salt, boneless	1.6	55.0	5.5	24.9	.3	..	14.3	510
Halibut, smoked	7.0	49.4	5.0	20.1	14.3	..	11.3	1015
Herring, smoked	44.4	34.6	5.2	35.8	15.0	..	9.9	1360
Mackeral, salt, dressed	19.7	43.4	5.0	16.8	25.1	..	9.7	1415
Salmon, canned	14.2	63.5	1.9	21.1	11.5	..	2.0	915
Sardines, canned	5.0	52.3	3.1	22.3	18.7	..	4.2	1250
Lobster, canned	..	77.8	1.3	17.6	1.0	.4	1.9	400
Clams, canned	..	82.9	1.0	10.2	.8	3.0	2.1	290
Oysters, canned	..	83.4	.8	8.5	2.3	3.9	1.1	340

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Animal Foods.	%	%	%	%	%	%	%	Calories.
Eggs.								
Eggs, uncooked	11.2	73.7	1.1	13.0	10.0	..	.8	695
Eggs, boiled	11.2	73.2	1.2	12.8	11.4	..	.6	755
Dairy products, etc.								
Whole milk	..	87.0	.5	3.2	3.8	5.0	.5	310
Skim milk	..	90.5	.3	3.3	.3	5.1	.5	170
Condensed milk, sweetened	..	26.9	1.2	8.5	7.9	54.1	1.4	1460
Cream	..	74.0	1.1	2.4	17.6	4.5	.4	860
Cheese	..	34.2	3.4	25.1	32.0	2.4	2.9	1885
Butter	..	11.0	4.9	1.0	80.8	..	2.3	3410
Oleomargarine, etc	..	9.5	5.7	1.2	78.9	..	4.7	3335
Lard, cottolene, etc	..	..	5.0	..	95.0	..	..	3985
Animal Food.								
Miscellaneous.								
Gelatin	..	13.6	3.2	88.7	.1	..	1.6	2125
Calf's-foot jelly	..	77.6	.3	4.2	..	17.4	.5	410
Vegetable Foods.								
Cereals, etc.								
Barley, pearled	..	11.5	4.0	6.6	1.0	76.1	.8	1630
Buckwheat flour	..	13.6	3.5	5.2	1.1	75.9	.7	1600
Buckwheat, self-raising	..	11.6	4.9	6.7	1.1	71.5	4.2	1545
Corn (maize) flour	..	12.6	3.6	5.8	1.2	76.3	.5	1625
Corn (maize) meal	..	12.5	4.0	7.5	1.7	73.5	.8	1625
Corn (maize) preparations:								
Cerealine	..	10.3	4.2	7.8	1.0	76.3	.4	1655
Hominy	..	11.8	3.8	6.8	.5	76.9	.2	1625
Hominy, cooked	..	79.3	.9	1.8	.2	17.4	.4	375
Oatmeal and rolled oats	..	7.8	5.6	13.4	6.6	65.2	1.4	1795
Oatmeal, boiled	..	84.5	.9	2.3	.5	11.3	.5	285
Rice	..	12.3	3.7	6.5	.3	76.9	.3	1610
Rice, boiled	..	72.5	1.1	2.3	.1	23.8	.2	505
Rye flour	..	12.9	3.6	5.3	.8	76.9	.5	1610
Entire wheat flour	..	11.4	4.5	10.7	1.7	70.9	.8	1645
Gluten flour	..	12.0	4.6	11.0	1.6	70.1	.7	1630
Graham flour	..	11.3	4.7	10.3	2.0	70.4	1.3	1640
Wheat flour, patent process:								
Low grade	..	12.0	4.5	10.9	1.7	70.2	.7	1635
Baker's grade	..	11.9	4.2	10.3	1.4	71.7	.5	1640

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Vegetable Foods.	%	%	%	%	%	%	%	Calories.
Cereals, etc.								
Family and straight grade	..	12.8	4.0	8.3	1.0	73.5	.4	1615
High grade	..	12.4	4.0	8.7	.9	73.6	.4	1620
Wheat preparations:								
Breakfast foods	..	9.6	4.5	9.3	1.6	74.0	1.0	1670
Macaroni	..	10.3	4.5	10.4	.8	73.0	1.0	1640
Macaroni, cooked	..	78.4	1.3	2.3	1.4	15.6	1.0	405
Spaghetti	..	10.6	4.0	9.4	.4	75.1	.5	1640
Noodles	..	10.7	4.2	9.1	.9	74.3	.8	1640
Bread:								
Brown	..	43.6	2.8	4.2	1.6	46.2	1.6	1035
Corn (johnnycake)	..	38.9	3.5	6.5	4.2	45.2	1.7	1170
Rye	..	35.7	3.4	7.3	.5	52.0	1.1	1160
Graham	..	35.7	3.4	6.9	1.6	51.3	1.1	1185
Whole wheat	..	38.4	3.2	7.5	.8	49.1	1.0	1125
White wheat	..	35.3	3.3	7.1	1.2	52.3	.8	1195
Biscuit, soda*	..	22.9	4.7	7.2	12.3	51.8	1.1	1655
Rolls	..	29.2	3.6	6.9	3.7	55.8	.8	1360
Toasted bread	..	24.0	4.1	8.9	1.4	60.3	1.3	1390
Crackers:								
Boston (split)	..	7.5	5.0	8.5	7.7	69.9	1.4	1830
Milk, cream	..	6.8	5.0	7.5	10.9	68.5	1.3	1920
Graham	..	5.4	4.8	7.7	8.5	72.5	1.1	1900
Oyster	..	4.8	5.4	8.8	9.5	69.3	2.2	1905
Soda	..	5.9	4.9	7.6	8.2	71.8	1.6	1870
Water	..	6.8	5.0	8.3	7.9	70.6	1.4	1850
Cakes, cookies, etc.:								
Bakers' cake	..	31.4	3.3	4.8	4.1	55.8	.6	1335
Coffee cake	..	21.3	3.8	5.5	6.8	61.9	.7	1580
Gingerbread	..	18.8	4.3	4.5	8.1	62.1	2.2	1620
Sponge cake	..	15.3	4.4	4.8	9.6	64.5	1.4	1735
Drop cake	..	16.6	4.5	5.9	13.2	59.2	.6	1805
Molasses cookies	..	6.2	4.7	5.6	7.8	74.0	1.7	1855
Sugar cookies	..	8.3	4.5	5.4	9.2	71.6	1.0	1865
Ginger snaps	..	6.3	4.7	5.0	7.7	74.3	2.0	1845
Wafers	..	6.6	4.8	6.7	7.7	73.0	1.2	1855
Doughnuts	..	18.3	4.8	5.2	18.9	52.1	.7	1895
Pie, pudding, etc.:								
Pie, apple	..	42.5	3.1	2.4	8.8	41.8	1.4	1215
Pie, custard	..	62.4	2.2	3.2	5.7	25.7	.8	795
Pie, squash	..	64.2	2.4	3.4	7.6	21.4	1.0	800

* Made from wheat flour, raised with baking powder.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Vegetable Foods.	%	%	%	%	%	%	%	Calories.
Cereals, etc.								
Pie, pudding, etc.:								
Pudding, Indian meal	..	60.7	2.5	4.5	4.3	26.9	1.1	785
Pudding, rice custard.	..	59.4	2.1	3.2	4.1	30.7	.5	825
Pudding, tapioca.....	..	64.5	1.0	2.8	2.9	28.2	.6	715
Sugars, starches, etc.								
Sugar, granulated.....	..	..	..	..	..	100.0	..	1790
Sugar, pulverized.....	..	..	..	..	..	100.0	..	1790
Sugar, brown.....	..	..	..	..	..	95.0	..	1700
Sugar, maple.....	..	..	..	..	..	82.8	..	1485
Molasses.....	..	..	..	..	..	70.0	..	1255
Maple syrup.....	..	..	..	..	..	71.0	..	1270
Cornstarch	..	..	..	..	..	90.0	..	1715
Tapioca.....	..	11.4	.1	.3	.1	88.0	.1	1685
Sago.....	..	12.2	1.4	7.7	.4	78.1	.2	1665
Vegetables.								
Asparagus, fresh.....	..	94.0	.7	1.3	.2	3.3	.5	95
Asparagus, cooked.....	..	91.6	1.0	1.7	3.0	2.1	.6	195
Beans, Lima, green.....	55.0	68.5	2.7	5.3	.6	21.6	1.3	525
Beans, Lima, dried.....	..	10.4	6.7	12.8	1.4	65.6	3.1	1565
Beans, string, fresh.....	7.0	89.2	1.0	1.7	.3	7.2	.6	180
Beans, string, cooked *...	..	95.3	.5	.6	1.0	1.9	.7	90
Beans, white, dried.....	..	12.6	7.5	15.8	1.6	59.9	2.6	1530
Beans, baked.....	..	68.9	2.8	4.8	2.3	19.6	1.6	565
Beets, fresh.....	20.0	87.5	1.0	1.2	.1	9.4	.8	205
Beets, cooked*.....	..	88.6	1.2	1.7	.1	7.2	1.2	170
Beet "greens," cooked*..	..	89.5	1.2	1.7	3.1	3.2	1.3	220
Cabbage.....	15.0	91.5	.7	1.2	.3	5.5	.8	140
Carrots, fresh.....	20.0	88.2	1.0	.7	.4	8.9	.8	200
Carrots, evaporated.....	..	3.5	6.9	5.8	3.2	76.9	3.7	1700
Cauliflower.....	..	92.3	.7	1.3	.5	4.7	.5	135
Celery.....	20.0	94.5	.6	.8	.1	3.2	.8	80
Sweet corn, green.....	61.0	75.4	1.8	2.3	1.0	19.0	.5	445
Cucumbers.....	15.0	95.4	.4	.6	.2	3.0	.4	75
Egg plant.....	..	92.9	.6	.9	.3	4.9	.4	120
Lettuce.....	15.0	94.7	.5	.9	.3	2.9	.7	85
Onions, fresh.....	10.0	87.6	.8	1.2	.3	9.6	.5	215
Onions, cooked*.....	..	91.2	.8	.9	1.6	4.8	.7	175
Parsnips.....	20.0	83.0	1.2	1.2	.5	13.0	1.1	290
Peas, dried.....	..	9.5	7.6	17.3	.9	62.5	2.2	1508

* With butter, etc., added.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrates.	Ash.	Fuel Value per lb. = 453.6 Grams.
Vegetable Foods.	%	%	%	%	%	%	%	Calories.
Vegetables.								
Peas, green	45.0	74.6	2.2	5.2	.5	16.7	.8	430
Peas, green, cooked*	..	73.8	2.5	5.1	3.1	14.4	1.1	490
Potatoes	20.0	78.3	1.4	1.7	.1	17.7	.8	370
Potatoes, cooked, boiled	..	75.5	1.7	1.9	.1	20.0	.8	415
Potatoes, mashed and creamed	..	75.1	2.0	2.0	2.7	17.1	1.1	475
Pumpkins	50.0	93.1	.6	.7	.1	5.0	.5	110
Radishes	30.0	91.8	.7	1.0	.1	5.6	.8	130
Rhubarb	40.0	94.4	.6	.4	.6	3.5	.5	100
Squash	50.0	88.3	.9	1.1	.5	8.6	.6	205
Spinach, fresh	..	92.3	1.0	1.6	.3	3.2	1.6	100
Spinach, cooked*	..	89.8	1.1	1.6	3.7	2.7	1.1	235
Sweet potatoes, fresh	20.0	69.0	2.1	1.3	.6	26.2	.8	545
Sweet potatoes, cooked*	..	51.9	3.0	2.2	1.9	40.3	.7	885
Tomatoes	..	94.3	.4	.7	.4	3.8	.4	100
Turnips	30.0	89.6	.8	1.0	.2	7.8	.6	175
Vegetables (canned).								
Asparagus	..	94.4	.6	1.2	.1	2.8	.9	80
Beans, baked	..	68.9	2.7	4.8	2.3	19.7	1.6	555
Beans, string	..	93.7	.7	.8	.1	3.7	1.0	90
Beans, Lima	..	79.5	1.7	3.0	.3	14.3	1.2	335
Sweet corn	..	76.1	1.7	2.1	1.1	18.3	.7	430
Peas, green	..	85.3	1.4	2.7	.2	9.6	.8	235
Succotash	..	75.9	1.8	2.7	.9	18.0	.7	425
Tomatoes	..	94.0	.5	.9	.2	3.9	.5	100
Fruits, etc. (fresh).								
Apples	25.0	84.6	1.6	.3	.5	12.8	.2	260
Apricots	6.0	85.0	1.5	.9	..	12.2	.4	240
Bananas	35.0	75.3	2.7	1.0	.5	19.9	.6	400
Blackberries	..	86.3	1.5	1.0	.9	9.9	.4	235
Cherries	5.0	80.9	2.0	.8	.7	15.1	.5	320
Cranberries	..	88.9	1.2	.3	.5	8.9	.2	190
Currants	..	85.0	1.7	1.2	..	11.6	.5	230
Figs	..	79.1	2.2	1.2	..	17.0	.5	330
Grapes	25.0	77.4	2.4	1.1	1.4	17.3	.4	390
Huckleberries	..	81.9	2.0	.5	.5	14.9	.2	300
Lemons	30.0	89.3	1.2	.8	.6	7.7	.4	180
Muskmelons	50.0	89.5	1.1	.5	..	8.4	.5	160
Oranges	27.0	86.9	1.4	.6	.2	10.5	.4	210

* With butter, etc., added.

COMPOSITION OF ORDINARY FOOD MATERIALS (Continued).

Kind of Food Material.	Inedible Refuse of Purchased Material.	Edible Portion.						
				Available Nutrients.				
		Water.	Unavailable Nutrients.	Protein.	Fat.	Carbohydrate.	Ash.	Fuel Value per lb. = 453.6 Grams.
Vegetable Foods.	%	%	%	%	%	%	%	Calories.
Fruits, etc. (fresh).								
Pears	10.0	84.4	1.7	.5	.4	12.7	.3	255
Plums	5.0	78.4	2.2	.8	..	18.2	.4	345
Prunes	6.0	79.6	2.1	.7	..	17.1	.5	325
Raspberries, black	..	84.1	1.7	1.4	.9	11.4	.5	270
Strawberries	5.0	90.4	1.0	.8	.5	6.8	.5	160
Watermelons	60.0	92.4	.9	.3	.2	6.0	.2	125
Fruits, etc. (dried).								
Apples	..	28.1	7.5	1.3	2.0	59.6	1.5	1190
Apricots	..	29.4	7.7	3.7	.9	56.5	1.8	1130
Citron	..	19.0	8.3	.4	1.3	70.3	.7	1340
Currants	..	17.2	8.6	1.9	1.5	67.0	3.8	1315
Dates	10.0	15.4	8.8	1.6	2.5	70.7	1.0	1415
Figs	..	18.8	8.7	3.4	.3	67.0	1.8	1290
Raisins	10.0	14.6	9.1	2.0	3.0	68.7	2.6	1410
Prunes	15.0	22.3	8.3	1.6	..	66.1	1.7	1230
Fruits, etc. (canned).								
Apricots	..	81.4	1.9	.7	..	15.7	.3	295
Blackberries	..	40.0	6.1	.6	1.9	50.9	.5	1015
Blueberries	..	85.6	1.6	.5	.5	11.5	.3	240
Cherries	..	77.2	2.3	.9	.1	19.1	.4	365
Crab-apples	..	42.4	5.7	.3	2.2	49.0	.4	985
Peaches	..	88.1	1.3	.5	.1	9.8	.2	190
Pears	..	81.1	1.9	.3	.3	16.2	.2	310
Strawberries (stewed)	..	74.8	2.6	.5	..	21.7	.4	400
Nuts.								
Almonds	45.0	4.8	10.9	17.8	49.4	15.6	1.5	2685
Butternuts	86.0	4.4	11.4	23.7	55.1	3.2	2.2	2805
Chestnuts (fresh)	16.0	45.0	5.9	5.3	4.9	37.9	1.0	990
Cocoanuts	49.0	14.1	9.2	4.8	45.5	25.1	1.3	2460
Filberts	52.0	3.7	10.7	13.3	58.8	11.7	1.8	2930
Hickorynuts	62.0	3.7	10.6	13.1	60.7	10.3	1.6	2980
Peanuts	25.0	9.2	10.7	21.9	34.7	22.0	1.5	2255

For greater detail see The Chemical Composition of American Food Materials, by Atwater and Bryant, Bulletin 28 (Revised), U. S. Dept. of Agriculture, Washington, 1902.

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